(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 November 2008 (13.11.2008)

PCT

(10) International Publication Number
WO 2008/134817 A1

(51) International Patent Classification:
A61K 47/26 (2006.01) *A61K 9/12* (2006.01)
A61K 9/14 (2006.01) *A61K 9/72* (2006.01)
A61P 11/00 (2006.01)

(21) International Application Number:
PCT/AU2008/000630

(22) International Filing Date: 5 May 2008 (05.05.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2007902336 3 May 2007 (03.05.2007) AU
2007903179 13 June 2007 (13.06.2007) AU

(71) Applicant *(for all designated States except US)*: **THE UNIVERSITY OF SYDNEY** [AU/AU]; Sydnovate, Level 5, SIT Building (J12), The University of Sydney, Sydney, New South Wales 2006 (AU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **YOUNG, Paul, Michael** [GB/AU]; 101 Darley Street, Newtown, NSW 2042 (AU). **CHAN, Hak-Kim** [AU/AU]; 8/220 Falcon Street, North Sydney, New South Wales 2060 (AU). **TRAINI, Daniela** [IT/AU]; 101 Darley Street, Newtown, NSW 2042 (AU).

(74) Agent: **F B RICE & CO**; Level 23, 44 Market Street, Sydney, NSW 2000 (AU).

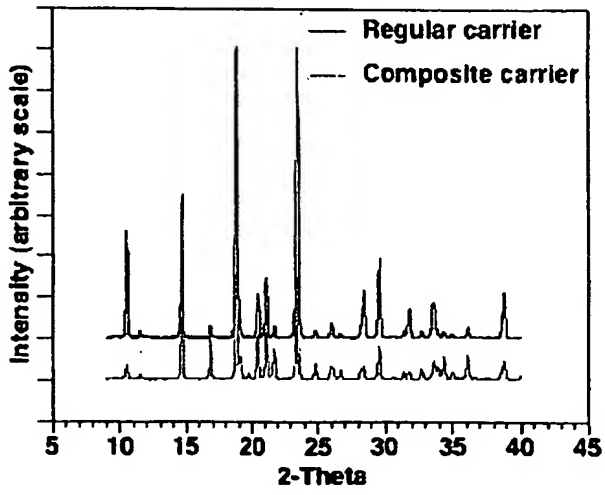
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: COMPOSITE CARRIERS FOR DRY POWDER INHALATION THERAPY

Figure 3 X-ray powder diffraction patterns of the regular and composite carrier particles.



(57) Abstract: The present invention comprises novel carrier particles formed from a plurality of adhered or otherwise co-joined sub-unit particles, which are suitable for aerosolisation. The present invention also relates to methods of forming drug carrier particles, and drug/carrier particle blends for use in dry powder inhalation therapy.

WO 2008/134817 A1

Published:
— *with international search report*

"Composite carriers for dry powder inhalation therapy"

Cross-Reference to Related Applications

The present application claims priority from Australian Provisional Patent Application No 2007902336 filed on 3 May 2007 and Australian Provisional Patent Application No 2007903179 filed on 13 June 2007, the contents of which are incorporated herein by reference.

Field of the Invention

The present invention relates to a drug carrier particle that is suitable for aerosolisation, a method of forming a drug carrier particle, and a drug/carrier particle blend for use in dry powder inhalation therapy.

Background of the Invention

Dry powder inhalation (DPI) drug therapy has been used for many years to treat respiratory conditions such as chronic obstructive pulmonary disease (COPD), bronchitis, allergy, rhinitis and asthma. Compared to oral drug intake, only relatively small doses are needed for effective therapy as first pass metabolism is significantly reduced. Such small doses reduce the body's exposure to the drug and minimise side effects. Systemic adverse effects are also reduced as topical lung delivery takes the drug directly to the site of action. Lower dosage regimens may also provide considerable cost savings, particularly where expensive therapeutic agents are concerned.

There is also growing interest in the use of lung drug delivery to treat non-pulmonary conditions. Because proteins and peptides have a rather poor absorption across the gastro-intestinal tract, the lung, with its large surface area, shows great promise for administering these substances. For example, insulin has been approved in at least some countries for inhalation therapy.

The success of DPI therapy depends on a number of factors including the biological aspect of the active ingredient, the physicochemical properties of the formulation, and the performance of the inhaler. The efficiency of dose delivery of dry

powders also depends on the particle size, size distribution, shape and surface morphology of the powder.

While considered optimal, drug particles having a size between 1 and 5 microns have a high surface area to mass ratio and therefore tend to be highly cohesive resulting in poor aerosolisation efficiency and thus respiratory deposition. As such, their delivery into the lung is usually enhanced when they are blended with larger and coarser inert crystalline carrier materials. Upon inhalation, the aim is for the drug particles to be freed from the carriers and to enter and penetrate the lung while the carriers themselves impact in the upper airways and are ingested.

The present invention is directed in part to formation of carrier particles that are suitable for use in dry powder inhalation therapy.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

Summary of the Invention

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

According to one aspect, the present invention is an inhalable drug carrier particle for carrying at least one drug particle, formed from a plurality of adhered or otherwise co-joined sub-unit particles, wherein the sub-unit particles have an average size of between about 20nm and about 20 microns.

By selecting sub-unit particles of this size, the resultant carrier particle may be advantageously used in inhalation therapy. The carrier particle adopts a different surface morphology to a carrier particle formed from crystalline carrier particles of a

similar size. It is believed that carrier particles formed from sub-unit particles with the size ranges discussed herein have advantageous properties when compared to carrier particles formed from larger sub-unit particles.

The term "inhalable drug carrier particle" is intended to encompass any carrier particle that is suitable for inhalation. Such a carrier particle would typically be used in an inhaler.

The sub-unit particles are adhered or otherwise co-joined to form the carrier particle. The term "adhered or otherwise co-joined" encompasses any form of binding the sub-units together. Various techniques for binding particles together are well known in the art and are encompassed by the present invention, including granulation techniques such as wet granulation.

The present invention relates to "average" sizes of particles. In one embodiment, the term "average size" can be replaced with the term "average diameter". In an further embodiment, the term "average size" can be replaced with the term "median size". In a yet further embodiment, the term "average size" can be replaced with the term "median diameter".

As discussed herein, the term "diameter" is a measure of the size of the particle. It is not limited to spherical particles and can be used to measure irregular particles. It may be considered the average length, width and/or height of the particles.

Preferably, the sub-unit particles have an average size of between about 20nm and about 15 microns, for example between about 2 and 15 microns. In one embodiment, the sub-unit particles can have an average size of about 3 microns, about 5 microns, about 7 microns, or about 10 microns. In a further embodiment, the carrier particle can be formed from at least one set of sub-unit particles having an average size of about 3 microns and at least one set of sub-unit particles having an average size of about 5 microns, 7 microns or 10 microns. Other combinations of sets of sub-unit particles can be envisaged.

In one embodiment, the sub-unit particles can have an average size of between about 1 and 15 microns. In a further embodiment, the sub-unit particles can have an average size of between about 2 and 12 microns. In a further embodiment, the sub-unit

particles can have an average size of between about 2 and 10 microns. In a further embodiment, the sub-unit particles can have an average size of between about 2 and 8 microns. In a further embodiment, the sub-unit particles can have an average size of between about 1 and 6 microns. In a further embodiment, the sub-unit particles can have an average size of between about 1 and 4 microns. In a further embodiment, the sub-unit particles can have an average size of between about 2 and 4 microns. In a further embodiment, the sub-unit particles can have an average size of between about 4 and 6 microns. In a further embodiment, the sub-unit particles can have an average size of between about 6 and 8 microns. In a further embodiment, the sub-unit particles can have an average size of between about 8 and 10 microns. The above numbered values are preferably +/- 1 micron, particularly preferably +/- 0.5 microns, particularly preferably +/- 0.2 microns, particularly preferably +/- 0.1 microns, or particularly preferably +/- 0.05 microns.

The sub-unit particles can have an average size of less than about 20 microns, preferably less than about 19 microns, preferably less than about 18 microns, preferably less than about 17 microns, preferably less than about 16 microns, preferably less than about 15 microns, preferably less than about 14 microns, preferably less than about 13 microns, preferably less than about 12 microns, preferably less than about 11 microns, preferably less than about 10 micron, preferably less than about 9 microns, preferably less than about 8 microns, preferably less than about 7 microns, preferably less than about 6 microns, preferably less than about 5 microns, preferably less than about 4 microns, preferably less than about 3 microns, preferably less than about 2 microns, preferably less than about 1 micron, preferably less than about 900nm, preferably less than about 800nm, preferably less than about 700nm, preferably less than about 600nm, preferably less than about 500nm, preferably less than about 400nm, preferably less than about 300nm, preferably less than about 200nm, preferably less than about 100nm, preferably less than about 50nm, preferably less than about 30nm.

In an alternative embodiment, the sub-unit particles are formed from particles wherein 90% of the particles ($d_{0.9}$) have an average size of less than about 20 microns, preferably less than about 19 microns, preferably less than about 18 microns, preferably less than about 17 microns, preferably less than about 16 microns, preferably less than about 15 microns, preferably less than about 14 microns, preferably less than about 13 microns, preferably less than about 12 microns, preferably less than about 11 microns, preferably less than about 10 microns, preferably less than about 9 microns, preferably

less than about 8 microns, preferably less than about 7 microns, preferably less than about 6 microns, preferably less than about 5 microns, preferably less than about 4 microns, preferably less than about 3 microns, preferably less than about 2 microns, preferably less than about 1 micron, preferably less than about 900nm, preferably less than about 800nm, preferably less than about 700nm, preferably less than about 600nm, or preferably less than about 500nm. In a further embodiment 80% of the particles ($d_{0.8}$), 70% of the particles ($d_{0.7}$), 60% of the particles ($d_{0.6}$), 50% of the particles ($d_{0.5}$), 40% of the particles ($d_{0.4}$), 30% of the particles ($d_{0.3}$), 20% of the particles ($d_{0.2}$), or 10% of the particles ($d_{0.1}$), are less than at least one of the abovementioned sizes.

In a further embodiment, the sub-unit particles can have an average size of 2 microns +/- 1 micron, preferably +/- 0.5 micron, particularly preferably +/- 0.2 micron, particularly preferably +/- 0.1 micron. In a further embodiment, the sub-unit particles can have an average size of 4 microns +/- 1 micron, preferably +/- 0.5 micron, particularly preferably +/- 0.2 micron, particularly preferably +/- 0.1 micron. In a further embodiment, the sub-unit particles can have an average size of 6 microns +/- 1 micron, preferably +/- 0.5 micron, particularly preferably +/- 0.2 micron, particularly preferably +/- 0.1 micron. In a further embodiment, the sub-unit particles can have an average size of 8 microns +/- 1 micron, preferably +/- 0.5 micron, particularly preferably +/- 0.2 micron, particularly preferably +/- 0.1 micron. In a further embodiment, the sub-unit particles can have an average size of 10 microns +/- 1 micron, preferably +/- 0.5 micron, particularly preferably +/- 0.2 micron, particularly preferably +/- 0.1 micron.

It can be seen that the present invention encompasses sub-unit particles of various sizes between about 20nm and about 20 microns. These sizes are similar to or smaller than the sizes of the drug particles the carriers are intended to carry.

Upon forming the carrier particle, the sub-unit particles may or may not remain the same size. Thus, before forming the carrier particle, the sub-unit particles may have an average size of between about 20nm and about 20 microns. These sub-unit particles are adhered or otherwise co-joined to form the carrier particle. Once the carrier particle has formed, it may still be possible to identify the individual sub-units from the fused carrier particle. These sub-units may still have an average size of between about 20nm and about 20 microns. However, it is possible that the size of the sub-unit particles will change as the carrier particle is formed due to fusing of the sub-units together or some

other mechanism. Equally, it may not be possible to distinguish the individual sub-unit particles when viewing the formed carrier particle. However, the surface properties of the carrier particle will have been, at least in part, affected by the choice of carrier particle.

The size of the sub-unit particle will affect aerosolisation efficiency and/or respiratory deposition.

In one embodiment, at least about 10% of the sub-unit particles forming the drug carrier particle have an average size of between about 20nm and about 20 microns. In a further embodiment, the drug carrier particle has at least about 20%, preferably about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, about 99%, about 99.5%, about 99.9%, or about 99.99% of the sub-unit particles having an average size of between about 20nm and about 20 microns. Equally, these sub-unit particles could have an average size of between about 20nm and 15 microns, about 2 and 12 microns, about 2 and 10 microns, less than about 12 microns, less than about 10 microns or any of the other sizes discussed herein.

The present invention includes carrier particles formed exclusively from sub-unit particles as discussed herein and equally carrier particles that have only a percentage of the sub-unit particles being sub-unit particles as discussed herein. The higher the percentage of sub-unit particles having an average size of between about 20nm and about 20 microns (or some other value as disclosed in the present invention), the more the properties of the final carrier particle will be affected by the choice of sub-unit particle. The skilled person will choose the amount of sub-unit particle having an average size as discussed herein to achieve the desired properties of the carrier particle.

The carrier particle itself may contain other excipients or ingredients as well as the sub-unit particles as discussed herein.

In one embodiment, the formed drug carrier particle has an average size of between about 50 to about 250 microns, more preferably between about 60 and about 100 microns, and even more preferably between about 63 and about 90 microns.

The choice of carrier particle size affects the performance of the aerosolised composition. In general, the size of the carrier particle will affect aerosolisation efficiency and respiratory deposition.

Therefore, in one embodiment there is provided an inhalable drug carrier particle formed from a plurality of adhered or otherwise co-joined sub-unit particles, wherein the drug carrier particle has an average size of about 50 and 250 microns, preferably between about 60 and about 100 microns, and more preferably between about 63 and about 90 microns.

According to a further preferred embodiment, the carrier particle formed from the plurality of sub-unit particles can have an average size of between about 50 to about 250 microns, and is formed from a plurality of sub-unit particles having an average size of between about 1 and 15 microns, preferably about 2 and 12 microns, about 2 and 10 microns, about 2 and 8 microns, about 1 and 6 microns, about 1 and 4 microns, about 2 and 4 microns, about 4 and 6 microns, about 6 and 8 microns, about 8 and 10 microns, all sizes +/- 1 micron, preferably +/- 0.5 microns, particularly preferably +/- 0.2 microns, particularly preferably +/- 0.1 microns.

According to a further preferred embodiment, the carrier particle formed from the plurality of sub-unit particles can have an average size of between about 60 and about 100 microns, and is formed from a plurality of sub-unit particles having an average size of between about 1 and 15 microns, preferably about 2 and 12 microns, about 2 and 10 microns, about 2 and 8 microns, about 1 and 6 microns, about 1 and 4 microns, about 2 and 4 microns, about 4 and 6 microns, about 6 and 8 microns, about 8 and 10 microns, all sizes +/- 1 micron, preferably +/- 0.5 microns, particularly preferably +/- 0.2 microns, particularly preferably +/- 0.1 microns.

According to a particularly preferred embodiment, the carrier particle formed from the plurality of sub-unit particles can have an average size of between about 63 and about 90 microns, and is formed from a plurality of sub-unit particles having an average size of between about 1 and 15 microns, preferably about 2 and 12 microns, about 2 and 10 microns, about 2 and 8 microns, about 1 and 6 microns, about 1 and 4 microns, about 2 and 4 microns, about 4 and 6 microns, about 6 and 8 microns, about 8 and 10 microns, all sizes +/- 1 micron, preferably +/- 0.5 microns, particularly preferably +/- 0.2 microns, particularly preferably +/- 0.1 microns.

It should be understood that when considering the size of the sub-unit particle or carrier particle, the bulk powder will contain a range of particle having different sizes. The present invention is concerned with the average size of the particle. Thus, for example, when forming sub-unit particles of 4 microns, the bulk powder will contain some particles of higher and lower sizes. However, the average particle size will be about 4 microns. Statistically, when preparing a batch of particles of a particular size, some of the formed particles will be considerably smaller or larger than the overall average size. These particles are to be expected and are encompassed by the present invention.

The particles are discussed with respect to their average size. The present invention is intended to encompass the "average" particle size. Thus, when mention is made of 10 micron particles, the present invention is intended to cover particles which, on average, have a size of about 10 microns. Obviously, some variation in particle size is to be expected when forming particles of this size and particles with an average size similar to that of the present invention are intended to fall within the scope of the invention. One measure of average sizes specifically encompassed by the present invention is the median average size.

In one embodiment, the particle can be formed by fusion of a plurality of sub-unit particles.

In one embodiment, the carrier particle is formed from sub-unit particles being each of substantially the same size. In another embodiment, the carrier particle is formed from sub-unit particles of different sizes. Still further, the carrier particle can be formed from a first set of sub-unit particles of substantially the same size and second or further sets of sub-unit particles, with each sub-unit particle in a set being of substantially the same size.

The properties of the carrier particle, including the surface properties can be adjusted by consideration of the choice of sub-unit particle. Either substantially all of the sub-unit particles forming the carrier particles fall within the scope of the present invention, or at least some of the particles do. Therefore, the present invention includes carrier particles formed from two or more sub-unit particles of different sizes, only one or some of which fall within the scope of the invention.

In one embodiment, the average size of the sub-unit particles is less than about 300% of the average size of the drug particle.

For example, if a drug particle has an average size of 6 microns, the carrier particle is preferably formed from sub-units having an average size of less than about 18 microns.

Thus, in one embodiment, the sub-unit particles are up to three times as large as the drug particles that are intended to be carried on the carrier particle. Therefore, one could determine the size of the drug particles intended to be carried on the carrier particle and then select sub-unit particles that are up to twice as big as the drug particle. Said another way, the present invention involves matching the size of the sub-unit particle to the size of the drug particle intended to be carried. The sub-unit particle may be larger, roughly the same size or smaller than the intended drug particle.

For what the inventors understand is the first time, the size of the drug particle has a direct impact on the choice of carrier particle.

Therefore, in one embodiment there is provided an inhalable drug carrier particle for carrying at least one drug particle, said drug carrier particle formed from a plurality of adhered or otherwise co-joined sub-unit particles, wherein the average size of the sub-unit particles is less than about 300% of the average size of the drug particle.

In one embodiment, the average size of the sub-unit particles is less than about 290% of the average size of the drug particle, preferably about 280%, 270%, 260%, 250%, 240%, 230%, 220%, 210%, 200%, 190%, 180%, 170%, 160%, 150%, 140%, 130%, 120%, 110%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20% or about 10%. In an alternative embodiment, the average size of the sub-unit particles is approximately the same as the average size of the drug particle. In a further alternative embodiment, the average size of the sub-unit particles is less than the average size of the drug particle.

In a further embodiment, the average size of the sub-unit particles is smaller than the average size of the drug particle. In one embodiment, the average size of the

sub-unit particles is 2 times smaller than the average size of the drug particle, preferably 3 times smaller, preferably 4 times smaller, preferably 5 times smaller, preferably 10 times smaller, preferably 20 times smaller, preferably 30 times smaller, preferably 50 times smaller, preferably 100 times smaller than the average size of the drug particle.

In one embodiment, the drug particle has an average size of less than about 7 microns, preferably, about 1 micron, about 2 microns, about 3 microns, about 4 microns, about 5 microns, about 6 microns or about 7 microns.

In one embodiment, the carrier particle can have a substantially homogeneous surface.

Prior art carrier particles suffered from the fact that the surface was very irregular. They could contain large crevices, multiple faces with different properties or highly irregular surfaces. This meant that a drug particle could not adhere to the surface of the carrier particle in a uniform manner. Some sections of the particle (for example crevices) would retain considerable drug particles whereas other sections would not. The same is true when considering respiratory deposition. Certain areas may retain the drug (for example crevices) which lowers the performance of the composition. Overall, having a highly irregular surface led to undesirable properties in the carrier particle and certainly made it difficult to design a carrier particle with specific properties.

In contrast, the surface of the present invention may be more homogenous than the prior art particles. By homogenous, it is meant that overall, there is less variation over the surface of the particle when considering one area compared with another. A given surface may in fact be considerably indented but this indentation is found more regularly over the whole surface of the particle than with prior art particles. A crystalline particle may have very flat surfaces which on the face of it appear homogenous. However, different surfaces will have markedly different electrostatic properties which will affect the adhering ability of the drug particle. The homogeneity of the present invention may help to give a more attractive adherence profile for the carrier particle.

In one embodiment, the carrier particle can have a relatively increased surface roughness. At least some, the majority, or all of the surface can be indented. The surface morphology may be adjusted for drug adhesion and drug delivery where required. In one embodiment, the adhesion of an active pharmaceutical ingredient to the carrier particle can be relatively spatially uniform. Where required, the surface morphology can be adjusted to suit the properties of the drug to be adhered.

Because the carrier particle is made up of a plurality of adhered or otherwise co-joined subunit particles, it may contain a large number of indentations, crevices or depressions between adjacent sub-units. For example, if the sub-unit particles are roughly spherical, the surface of the carrier particle may contain depressions or gaps between each sub-unit. The size of these depressions can be controlled by the size and/or shape of the sub-unit particles. Smaller sub-unit particles will give rise to smaller gaps between adjacent particles whereas larger sub-unit particles will not only giver wider but also deeper indentations.

Such gaps may be useful in modifying the adhesion properties of the drug particle adhered to the carrier particle. For example, a drug particle will have a higher contact area if adhered to a flat uniform surface. However, if the surface contains indentations or gaps, the drug particle will have a lower contact area due to increased void spaces. This affects how strongly the drug particle adheres to the surface of the carrier. A minimum level of adherence is desired to enable the drug particles to be carried on the carrier particle. However, the adherence level should not be too high so as to make it difficult for the drug particle to be removed from the carrier particle during respiratory deposition.

One way to control this adherence is to modify the gaps between the sub-unit particles. Wider and/or more frequent gaps will result in a lower contact area and adherence value for the carrier particle. Selection of the sub-unit particle size will change the frequency and size of the gaps.

Therefore, in one embodiment, there is provided an inhalable drug carrier particle for carrying at least one drug particle, said drug carrier particle formed from a plurality of adhered or otherwise co-joined sub-unit particles, wherein the average size of the gaps between the co-joined sub-unit particles on the surface of the drug carrier particle is less than the average size of the drug particle. Alternatively, the average size

of the gaps are roughly the same size as the diameter of the drug particle. A further alternative is that the gaps are slightly larger than the average size of the drug particle.

The average gap size may be thought of as the diameter of the gap, that is the average size from one side of the gap to the other.

If the gaps between the sub-unit particles are similar in size or smaller than the average size of the drug particle, the drug particles are less likely to be present or fall into these gaps and become stuck or at least relatively more difficult to dislodge. Introducing crevices has been a specific design feature of prior art carrier particles as it was believed that producing crevices on the surface of the carrier particle helped to adhere a greater number of drug particles onto the carrier. However, in practice, it is believed that many of these drug particles lodged in the crevices remain with the carrier particle and do not reach the lungs of the patient. These crevices were of such a size that drug particles would fall into them and become trapped. It is believed that these drug particles may not be liberated from the carrier. Thus, while the traditional carrier particles show good adherence for the drug particles, many of these particles will have no clinical benefit for the patient.

By ensuring that some or most of the gaps on the surface of the carrier particle are similar in size or smaller than the drug particle, this problem may be avoided. Thus, the drug may particles substantially sit on the surface of the carrier particle rather than fall within crevices formed from prior art particles.

Therefore, by ensuring that the surface of the carrier particle contains fewer crevices that are of a size larger than the drug particles, more drug particles will sit on the surface of the carrier. This is believed to improve performance.

In one embodiment, about 10%, preferably, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, about 99% or about 99.9% of the gaps on the surface of the carrier particle have an average size less than the average size of the drug particle.

In one embodiment, about 10%, preferably, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, about 99% or about 99.9% of the gaps on the surface of the carrier particle have an

average size of less than about 12 microns, preferably less than about 10 microns, about 8 microns, about 6 microns, about 4 microns, about 2 microns, about 1 microns, about 900nm, about 800nm, about 700nm, about 600nm, about 500nm, about 400nm, about 300nm, about 200nm, about 100nm, about 50nm, about 20nm, about 10nm or about 5nm.

The gaps between the sub-unit particles are preferably about 150%, 140%, 130%, 120%, 110%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, or 5% the average size of the drug particles.

The sub-unit particles as discussed herein preferably give rise to surface gaps on the carrier particle substantially as described above.

When considering the surface of carrier particles, various theoretical surface types are possible. A theoretical smooth carrier surface would give a high contact area between the carrier particle and the drug particle. Such a carrier would give good uniformity over the surface of the carrier. However, such a carrier would have a high level of adhesion and would therefore give poor drug liberation. Such a theoretical carrier is difficult to produce commercially.

Typical commercial grade carriers have a highly varied carrier surface and are typically low cost. However, there is considerable variation in contact area over the surface of the particle which results in considerable drug liberation variation. In addition, it is not possible to tailor the surface properties.

If the carrier surface has regular indentations it will give a more uniform surface since the surface will be similar over the entire particle. This contrasts with commercial carriers and would give a consistent adhesion profile and uniformity. However, if the indentations are significantly larger than the drug particle individual drug particles will still have high contact with the carrier since they effectively "see" a smooth surface. The surface can be thought of as rolling hills with drug particles adhered over the entire surface of the carrier. This may give rise to high adhesion between the drug and the carrier and poor drug liberation..

If the surface contains uniform gaps and the gaps are smaller than the drug particles then the surface will be uniform giving a consistent adhesion. The gaps create

void spaces which reduce the contact area. This can help to increase drug liberation. Such a surface is ideal as the contact area and adhesion profile is uniform and controllable.

If the void spaces reduce the contact area too far, the adhesion decreases to a point where the carrier becomes less useful as it cannot adhere enough drug particles.

In one embodiment, the carrier particles have a granular surface morphology.

In one embodiment, the carrier particle has a substantially uniform surface roughness.

A measure of surface roughness is the root mean square roughness (R_{RMS}). This is calculated using Equation 1.

Equation 1 $$R_{rms} = \sqrt{\frac{1}{n}\sum_{i=1}^{n} y_i^{\,2}}$$

According on one embodiment, the carrier particle has an R_{RMS} of about >0.1nm, preferably >0.2nm, preferably >0.3nm, preferably >0.4nm, preferably >0.5nm, preferably >0.6nm, preferably >0.7nm.

According to one embodiment, the carrier particle has an adhesion value (preferably average force value $f_{0.5}$) of about <110nN, preferably about <100nN, more preferably about <90nN, more preferably about <80nN, more preferably about <70nN, more preferably about <60nN, more preferably about <50nN, more preferably about <40nN, more preferably about <30nN, more preferably about <20nN, more preferably about <10nN. Preferably, the carrier particle has an adhesion value (average force value $f_{0.5}$) of between about 10nN and about 110nN, preferably between about 10nN and 90nN, preferably between about 20nN and 70nN, preferably between about 20nN and 60nN, preferably between about 20nN and 50nN, preferably between about 20nN and 40nN, preferably between about 30nN and 50nN.

The spread of force values (adhesion values) can be calculated from the geometric standard deviation:

Equation 2 $$GSD = \left[\frac{f_{0.84}}{f_{0.16}}\right]^{0.5}$$

Where f_x are the respective percentile force values for the lognormal distribution.

In one embodiment, the carrier particle has a GSD value of about < 1.88, preferably about < 1.85, preferably about < 1.80, preferably about < 1.78, preferably about < 1.76, preferably about < 1.75, preferably about < 1.73, preferably about < 1.71, preferably about < 1.69, preferably about < 1.68, preferably about < 1.67. In one embodiment, the GSD value is <1.6, preferably <1.5, preferably <1.4, preferably <1.3, preferably <1.2 or preferably <1.1.

In one embodiment, the coefficient of variation (CV) of the GSD is less than about 10%, preferably less than about 8%, preferably less than about 7%, preferably less than about 6%, preferably less than about 5%, preferably less than about 4%, preferably less than about 3%.

The carrier particle may give improved aerosolisation efficiency. In one embodiment, the carrier particle gives rise to a fine particle fraction (FPF) of greater than about 20%, preferably greater than about 22%, preferably greater than about 24%, preferably greater than about 26%, preferably greater than about 28%, preferably greater than about 30%, preferably greater than about 32%, preferably greater than about 34%. In a further embodiment, the carrier particle gives rise to a fine particle fraction (FPF) of greater than about 40%, preferably greater than about 50%, preferably greater than about 60%, preferably greater than about 70%, preferably greater than about 80%, preferably greater than about 90%, preferably greater than about 95%, preferably greater than about 98%, preferably greater than about 99%.

In one embodiment, the carrier particle gives rise to a reduced contact geometry for the adhered drug.

In one embodiment there is provided an inhalable drug carrier particle formed from a plurality of adhered or otherwise co-joined particle engineered sub-unit particles. The sizes, surface properties and other features as discussed herein are applicable to these sub-unit particles and drug carrier particles. In particular, at least

about 10% of the particles forming the drug carrier particle are particle engineered sub-unit particles. Preferably, at least about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, about 99%, about 99.5%, about 99.9%, or about 99.99% of the particles forming the drug carrier particle are particle engineered sub-unit particles. These sub-unit particles could have an average size of between about 20nm - 15 micron, 2-12 micron, 2-10 micron, less than 12 micron, less than 10 micron or any of the other sizes discussed herein.

In one embodiment there is provided a drug/carrier particle blend formed from drug carrier particles as discussed herein.

The carrier particles may be composed of any pharmacologically inert material or combination of materials which is acceptable for inhalation. They are suitably composed of one or more sugars including monosaccharides, disaccharides, polysaccharides such as arabinose, glucose, fructose, ribose, mannose, sucrose, trehalose, lactose, maltose, dextran, starches and sugar alcohols such as mannitol or sorbitol and mixtures of two or more thereof. A preferred diluent or carrier is lactose, particularly in the form of the monohydrate. An alternate carrier is mannitol.

In one embodiment, a plurality of carrier particles can be loaded with a drug or active pharmaceutical ingredient to form a drug/carrier particle blend. A quantity of such a blend can then be loaded into a capsule or any container ready for aerosolisation and delivery to the respiratory tract of a patient. Other pharmaceutically acceptable excipients, diluents and/or adjuvants can be added to the capsule or container if desired. The adhesion between the drug and the carrier particle is preferably such to ensure a stable ordered mix of the blend whilst being low enough to allow drug liberation during inhalation.

Examples of drugs which can be used with the carrier particle of the present invention include beta-2 agonists, anticholinergics, mast cell stabilisers, steroids, methylxanthines, inhaled corticosteroids, cromolyn and nedocromil, theophylline, leukotriene modifiers long-acting beta-2 agonists, short-acting beta-2 agonists and/or systemic corticosteroids.

Specific examples of drugs which can be used with the carrier particle of the present invention include acetonide, albuterol, albuterol sulfate, beclomethasone,

budesonide, cortisone, cromolyn sodium, dexamethasone, flunisolide, fluticasone, formoterol, formoterol fumarate, hydrocortisone, pratropium, ipratropium / albuterol, levalbuterol HCl, metaproterenol, methylprednisolone, mometasone, montelukast, nedocromil sodium, omalizumab, pirbuterol, prednisolone, propionate, salbutamol, salmeterol, salmeterol xinafoate, terbutaline, theophylline, tiotropium, triamcinolone, zafirlukast or zileuton.

"Drugs", for the purposes of the invention, include a variety of pharmaceutically active ingredients, such as, for example, those which are useful in inhalation therapy. In general, the term "drug" is to be broadly construed and include, without limitation, actives, drugs and bioactive agents, as well as biopharmaceuticals.

The term "drug" is interchangeable with the term medicament.

Various embodiments may include drugs present in micronized form or soluble form. Appropriate drugs may thus be selected from, for example, analgesics, (e.g., codeine, dihydromorphine, ergotamine, fentanyl or morphine); anginal preparations, (e.g., diltiazem); anti-allergies, (e.g., cromoglicate, ketotifen or nedocromil); antiinfectives (e.g., cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine); antihistamines, (e.g., methapyrilene); antiinflammatories, (e.g., anti-inflammatory steroids, beclomethasone (e.g. beclomethasone dipropionate), fluticasone (e.g. fluticasone propionate), flunisolide, budesonide, rofleponide, mometasone (e.g. mometasone furoate), ciclesonide, triamcinolone (e.g. triamcinolon acetonide), 6α, 9α-difluoro-11 β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothioic acid, S-(2-oxo-tetrahydro-furan-3-yl)ester), (6a,11b,16a,17a)-6,9-difluoro-17-{[(fluoromethyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 2-furoate, and (6a,11b,16a,17a)-6,9-difluoro-17-{[(fluoromethyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 4-methyl-1 ,3-thiazole-5-carboxylate); antitussives, (e.g., noscapine); bronchodilators, (e.g., albuterol (e.g., as sulphate), salbutamol (e.g., as the free base or the sulphate salt), salmeterol (e.g., as xinafoate), ephedrine, adrenaline, fenoterol (e.g., as hydrobromide), bitolterol, formoterol (e.g., as fumarate), isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol (e.g., as acetate), reproterol (e.g., as hydrochloride), rimiterol, terbutaline (e.g., as sulphate), isoetharine, tulobuterol, 4-hydroxy-7-[2-[[2-[[3-(2-(henylethoxy)propyl]sulfonylurea]ethyl]-amino]ethyl-2(3H)-benzothiazolone), 3-(4-{[6-({(2R)-2-hydroxy-2-[4-hydroxy-3-

(hydroxymethyl) phenyl]ethyl}amino)hexyl]oxy}butyl)benzenesulfonamide, 3-(3-{[7-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)heptyl]oxyjpropyl) benzenesulfonamide, 4-{(1R)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy] ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol, 2-hydroxy-5-((1 R)- 1-hydroxy-2-{[2-(4-{[(2R)-2-hydroxy-2-phenylethyl]amino}phenyl)ethyl]amino}ethyl)phenylformamide, and 8-hydroxy-5-{(1R)-1-hydroxy-2-[(2-{4-[(6-methoxy-1,1'-biphenyl-3-yl)amino]phenyl}ethyl)amino]ethyl}quinolin-2(1H)-one); diuretics, (e.g., amiloride) ; anticholinergics, (e.g., ipatropium (e.g., as bromide), tiotropium, atropine or oxitropium); hormones, (e.g., cortisone, hydrocortisone or prednisolone); xanthines, (e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline); therapeutic proteins and peptides, (e.g., insulin). In addition to those stated above, it will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts, (e.g., as alkali metal or amine salts or as acid addition salts) or as esters (e.g., lower alkyl esters) or as solvates (e.g., hydrates) to optimize the activity and/or stability of the medicament. It will be further clear to a person skilled in the art that where appropriate, the medicaments may be used in the form of a pure isomer, for example, R-salbutamol or R-formoterol. Particular medicaments for administration using pharmaceutical formulations in accordance with the invention include anti-allergies, bronchodilators, beta agonists (e.g., long-acting beta agonists), and anti-inflammatory steroids of use in the treatment of respiratory conditions, as defined herein, by inhalation therapy, for example, cromoglicate (e.g. as the sodium salt), salbutamol (e.g. as the free base or the sulphate salt), salmeterol (e.g. as the xinafoate salt), bitolterol, formoterol (e.g. as the fumarate salt), terbutaline (e.g. as the sulphate salt), 3-(4-{[6-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)benzenesulfonamide, 3-(3-{[7-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)heptyl]oxy}propyl)benzenesulfonamide, 4-{(1 f?)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy] ethoxy}hexyl)amino]-1 -hydroxyethyl}-2-(hydroxymethyl)phenol, 2-hydroxy-5-((1 R)- 1-hydroxy-2-{[2-(4-{[(2R)-2-hydroxy-2-phenylethyl]amino}phenyl)ethyl]amino} ethyl)phenylformamide, 8-hydroxy-5-{(1 R)-1 -hydroxy-2-[(2-{4-[(6-methoxy-1 ,V- biphenyl-3-yl)amino]phenyl}ethyl)amino]ethyl}quinolin-2(1 H)-one, reproterol (e.g. as the hydrochloride salt), a beclomethasone ester (e.g. the dipropionate), a fluticasone ester (e.g. the propionate), a mometasone ester (e.g., the furoate), budesonide, dexamethasone, flunisolide, triamcinolone, tripredane, (22R)-6α,9α- difluoro-11 β, 21 -

dihydroxy-16α,17α-propylmethylenedioxy-4-pregnen-3,20-dione. Medicaments useful in erectile dysfunction treatment (e.g., PDE-V inhibitors such as vardenafil hydrochloride, along with alprostadil and sildenafil citrate) may also be employed. It should be understood that the drugs that may be used in conjunction with the inhaler are not limited to those described herein.

Salmeterol, especially salmeterol xinafoate, salbutamol, fluticasone propionate, formoterol, budesonide, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof are especially preferred.

It will be appreciated by those skilled in the art that the formulations according to the invention may, if desired, contain a combination of two or more of any of the above drugs. As an example, formulations containing two active ingredients are known for the treatment and/or prophylaxis of respiratory disorders such as those described herein, for example, formoterol (e.g. as the fumarate) and budesonide, salmeterol (e.g. as the xinafoate salt) and fluticasone (e.g. as the propionate ester), salbutamol (e.g. as free base or sulphate salt) and beclomethasone (as the dipropionate ester) are preferred.

According to a further aspect, the present invention is a method of forming an inhalable drug carrier particle comprising:

a) particle engineering a substance to form sub-unit particles;

b) adhering or otherwise co-joining the sub-unit particles to form the drug carrier particle.

By particle engineering, we mean processes of forming sub-unit particles of a particular size. In one embodiment, we mean processes of reducing the size of particles into smaller sub-units, i.e. particle size reduction. Particle engineering processes includes spray drying, micronisation, freeze drying, crystallisation through sonication, high gravity precipitation, impinging jet precipitation, spray freeze drying, and supercritical fluid precipitation among others.

The term particle engineering is intended to cover any process by which small particles are formed. The particles preferably end up with an average size of between about 20nm and about 20 microns although the term encompasses all of the sizes discussed herein in relation to sub-unit particles.

Examples of particle engineering include using a spray drying process using a spray dryer in which solutions of the material making up the particles are spray dried. Alternative methods of sub-unit particle manufacture can be used, including crystallisation, micronisation, or any suitable method for producing micro and/or nanoparticles.

According to a yet further aspect, the present invention is a method of forming an inhalable drug carrier particle for carrying at least one drug particle, said method comprising:

a) using sub-unit particles with an average size of less than about 200% of the average size of the drug particle;

b) adhering or otherwise co-joining the sub-unit particles to form the drug carrier particle.

The methods discussed herein can preferably use the sub-unit particles discussed herein. Furthermore, the methods discussed herein preferably form drug carrier particles with at least one of the properties discussed herein.

Thus, there is provided in one embodiment, a method of forming a drug carrier particle comprising preparing sub-unit particles as discussed herein and binding or fusing the particles together to form the carrier particle.

As discussed above, the sub-unit particles can be formed using a spray drying process using a spray dryer in which solutions of the material making up the particles are spray dried. Alternative methods of sub-unit particle manufacture can be used, including crystallisation, micronisation, or any suitable method for producing micro and/or nanoparticles.

In one embodiment of this aspect, the carrier particle is formed from sub-unit particles being each of substantially the same size. In another embodiment, the carrier particle is formed from sub-unit particles of different sizes. Still further, the carrier particle can be formed from a first set of sub-unit particles of substantially the same size and second or further sets of sub-unit particles, with each sub-unit particle in a set being of substantially the same size.

The different sub-unit particle sizes can be obtained through control of the process used to form the particles, including the processes defined herein. In regard to the spray drying process, such control can include controlling such features as the concentration of the solution, the inlet temperature at the spray dryer, the aspirator speed, the liquid flow rate and the atomisation pressure.

In one embodiment of this aspect, the sub-unit particles can have an average size of between about 20nm and about 15 microns, for example between about 2 and about 15 microns. In one embodiment, the sub-unit particles can have an average size of about 3 microns, about 5 microns, about 7 microns, or about 10 microns. In a further embodiment, the carrier particle can be formed from at least one set of sub-unit particles having an average size of about 3 microns and at least one set of sub-unit particles having an average size of about 5 microns, 7 microns or 10 microns. In a further embodiment, the sub-unit particles can be any of the sizes discussed herein (particularly as discussed on pages 3-6).

The carrier particles can be formed from a slurry containing a saturated solution of sub-unit particles. Techniques such as spheronisation, spray drying and granulation can be used to form the carrier particles. For example, the slurry can be dried in an oven and fractionated through a series of sieves to form carrier particles having a desired size.

In this embodiment, the carrier particles formed from the plurality of sub-unit particles can have an average size of between about 50 to about 250 microns, more preferably between about 60 and about 100 microns, and even more preferably between about 63 and about 90 microns.

In one embodiment, the formed carrier particle can have a substantially homogeneous surface. In one embodiment of this aspect, the carrier particle can have a relatively increased surface roughness. At least some, the majority or all of the surface can be indented. The surface morphology can be suitable for drug adhesion and drug delivery when required. In one embodiment, the adhesion of an active pharmaceutical ingredient to the carrier particle can be relatively spatially uniform. Where required, the surface morphology can be adjusted to suit the properties of the drug to be adhered to the carrier particle.

In this aspect, the carrier particle can be formed of sub-unit particles of any suitable material, including mannitol, lactose, and other sugars.

A mixing process can be used to load the formed carrier particles with the selected drug. The drug can be micronised prior to mixing with the carrier particles to form a drug/carrier particle blend.

One example of a drug/carrier particle blend can be formed using salbutamol sulphate in a ratio of about 67.5:1 carrier:drug.

Where the drug is to be aerosolised, the drug/carrier particle blend can be loaded into a suitable capsule or container, such as a gelatine capsule. The capsule can also be loaded if required with other pharmaceutically acceptable excipients, diluents and/or adjuvants. The adhesion between the drug and the carrier particle is preferably such to ensure a stable ordered mix of the blend whilst being low enough to allow drug liberation during inhalation.

According to a still further aspect, the present invention is a method of delivering a drug to a patient requiring the drug comprising forming a drug/carrier particle blend as defined herein and aerosolising the blend such that it is suitable for inhalation by the patient.

According to a further aspect, a plurality of carrier particles are loadable with a drug to form a drug/carrier particle blend.

According to a further aspect, the present invention is a drug/carrier particle blend formed from carrier particles as defined herein.

The drug/carrier particle blend can be formed using the method as defined herein.

According to yet another aspect, the present invention comprises a method of delivering a drug to a patient requiring the drug, the method comprising forming a drug/carrier particle blend as defined herein and aerosolising the blend such that it is suitable for inhalation by the patient.

Where mention is made of a drug herein, the present invention encompasses a plurality of drugs.

Such aerosolisation techniques are well known in the art and all suitable methods are encompasses herein.

According to yet another aspect, the present invention comprises a method of treating a patient having a respiratory or non-respiratory condition, said method comprising administering the drug/carrier particle blend as defined herein.

Respiratory conditions include, COPD, bronchitis, allergy, rhinitis, cystic fibrosis, pulmonary infection and asthma.

According to yet another aspect, the present invention comprises use of the drug/carrier particle blend as defined herein in the manufacture of a medicament for treatment of a respiratory or non-respiratory condition of a patient.

In one embodiment, the respiratory condition can be COPD, bronchitis, allergy, rhinitis, cystic fibrosis, pulmonary infection and asthma.

The medicament can be manufactured using the methods as defined herein.

In one embodiment, there is provided an inhalation drug carrier particle for carrying at least one drug particle, said drug carrier particle formed from a plurality of adhered or otherwise cojoined sub-unit particles, wherein the average size of the sub-unit particle is selected such that, in use, the:

a) surface topography;
surface roughness;
surface uniformity;
surface homogeneity; and/or
surface cohesion force of the drug carrier particle; and/or

b) the contact geometry; and/or
adhesion force of the drug carrier particle relative to the drug particle; and/or

c) the fine particle fraction of the drug particle carried on the drug carrier particle;

is optimised to enhance the aerosol performance of the drug/carrier particle blend.

In one embodiment, there is provided a method for forming an inhalation drug carrier particle for carrying at least one drug particle, said drug carrier particle formed from a plurality of adhered or otherwise cojoined sub-unit particles comprising selecting an average size of the sub-unit particles such that, in use, the:

a) surface topography;
surface roughness;
surface uniformity;
surface homogeneity; and/or
surface cohesion force of the drug carrier particle; and/or

b) the contact geometry; and/or
adhesion force of the drug carrier particle relative to the drug particle; and/or

c) the fine particle fraction of the drug particle carried on the drug carrier particle;

is optimised to enhance the aerosol performance of the drug/carrier particle blend.

Brief Description of the Drawings

By way of example only, preferred embodiments of the invention are now described with reference to the following drawings, in which:

Fig. 1 is a graph of particle size distribution of the sub-unit particles formed to manufacture the carrier particles according to the present invention;

Fig. 2 is a graph of particle size distribution of carrier particles formed from the sub-unit particles defined herein, raw mannitol carrier, and micronised salbutamol sulphate;

Fig. 3 depicts X-ray powder diffraction patterns of regular carrier particles (i.e. not formed in accordance with the present invention) and composite carrier particles according to the present invention;

Fig. 4 depicts scanning electron micrographs of 63-90 micron sieve fractionated (A) raw crystalline mannitol, (B) 3 micron, (C) 5 micron and (D) 10 micron carrier particles;

Figs. 5A and 5B are representative atomic force microscope topographic images of a regular carrier and a composite carrier;

Fig. 6 depicts the spatial adhesion distribution of salbutamol sulphate drug probe 1 over 10 x 10 μm areas of a regular and composite carrier;

Fig. 7A depicts the cumulative percentage adhesion plot for salbutamol AFM probe 1 measured over a 10 x 10 μm area on a regular and composite carrier (as in Fig. 5) and Fig. 7B depicts the median separation force of three probes on both carrier substrates;

Fig. 8 is a graph of the aerosolisation efficiency of salbutamol sulphate from different drug/carrier particle blends measured as fine particle fraction (FPF);

Fig. 9 represents next generation impactor stage deposition of salbutamol sulphate aerosolised from blends containing each of the carriers;

Fig. 10 provides high magnification SEM images of (A) regular carrier blend and (B) composite carrier blend with the arrows pointing to likely salbutamol sulphate particulates;

Fig. 11 is a graph of particle size distributions of the (A) micronised drug samples and primary lactose particles (median) and (B) carrier particles (sieved);

Fig. 12 provides scanning electron microscopy images of fractioned (A) regular carrier, (B) 2 μm based carrier, (C) 6 μm based carrier and (D) 10 μm based carrier;

Fig. 13 provides representative topographical images of the 63-90 μm sieve fractioned (A) regular carrier (B) 2 μm based carrier (C) 6 μm based carrier and (D) 10 μm based carrier;

Fig. 14 provides X-ray powder difractographs for the (A) primary lactose particles and (B) carriers;

Fig. 15 provides differential scanning calorimetry thermograms of (A) primary lactose particles and (B) carriers;

Fig. 16 provides an adhesion distribution matrix (10 μm x 10 μm areas) for a single salbutamol probe on each carrier lactose. Mean GSD values are given for n=3 probes with standard deviations and % CV;

Fig. 17 shows the *in vitro* NGI stage deposition of salbutamol sulphate aerosolised from each of the carriers;

Fig. 18 shows the *in vitro* aerosol performance (FPF) as a function of roughness (R_{RMS}). Error bars indicate standard deviations (n=3);

Fig. 19 provides a graph showing the relationship between median adhesion force (n=3 tips ± StDev) and the aerosol efficiency (FPF%, n=3); and

Fig. 20 provides schematic views of different carrier particle morphologies and the predicted influence of this on drug particle adhesion.

Preferred Mode of Carrying out the Invention

The following description describes methods of forming carrier particles from a plurality of adhered, fused or otherwise co-joined sub-unit particles of mannitol and lactose. It will be appreciated that other materials, such as other sugars, can be utilised to form suitable carrier particles.

The carrier particles as formed herein can be used to form drug/carrier particle blends that are suitable for inhalation by a patient requiring the drug. The drug can be suitable for treating respiratory conditions such as cystic fibrosis, COPD, bronchitis, allergy, rhinitis and asthma. It will also be appreciated that the drug can be suitable for delivery via the lungs and be used to treat non-pulmonary conditions.

Mannitol as the Carrier Particle

In the presently described embodiment, mannitol sub-unit particles of approximately 3, 5, and 10 micron diameter were prepared by spray drying aqueous

mannitol solutions through a laboratory scale Büchi-191 Mini Spray Dryer. The different particle sizes were obtained by carefully controlling the spray drying conditions, including the mannitol concentration, the inlet temperature, the aspirator speed, the liquid flow rate and the atomisation pressure. For example, to prepare mannitol particles with a diameter of approximately 3 microns, the particles were produced by spray drying a 5 mg/ml aqueous mannitol solution using the Büchi-191 Mini Spray Dryer with the following settings: inlet temperature = 110°C, solution feed rate = 1.25 ml/min, compressed air pressure = 800 kPa, aspirator = 100% and observed outlet temperature = 62°C.

The sizes of the formed sub-unit particles were measured by laser diffraction. Fig. 1 depicts the particle size distribution of the formed mannitol sub-unit particles.

Once formed, the sub-unit particles were used to form a series of different larger composite carrier particles. As described below, different carrier particle combinations were formed from the different groups of sub-unit particles. It will be appreciated that carrier particles could be formed, if desired, from sub-unit particles of different diameters.

In this example, composite carriers were produced using a wet granulation method in which different slurries were made. Each was made from only one size of the primary spray-dried mannitol particles. Saturated mannitol was used as the binder and constituted no more than 10% v/w of the total slurry. The slurries were dried and sieve fractionated (e.g. through a 180 microns sieve) to obtain a 63-90 microns diameter carrier particle formulation. The particle size distribution of the composite carrier particles were confirmed by laser diffraction (see Fig. 2).

The crystallinity of the carrier particles and a regular carrier not formed according to the method of the present invention were each assessed using X-ray powder diffraction (XRPD, D5000, Siemens, Germany) at room temperature using a Cu Kα radiation at 30 mA and 40 kV, with an angular increment of 0.05°/s and count time of 2s. The results of the X-ray diffraction are presented in Fig. 3, with the patterns produced being characteristic of a crystalline material.

The particle morphology was investigated optically using a stereo-microscope at 100x magnification (CX41 microscope with DP12 digital camera, Olympus, Japan).

Particles were deposited on a microscope slide and dispersed in paraffin oil before a cover slip was added. Wide field images were collected and exported to Image-J software (www.NIH.gov). Images were processed by threshold analysis to produce a projected particle image where particle area P_A, particle perimeter P_P, particle length P_L and particle width P_W could be measured. The data was analysed (n = 50 for each carrier) and the following shape descriptors calculated: elongation ratio (P_L/P_W) and shape factor ($4\pi \times P_A/P_P^2$). Elongation ratios of 2.08 ± 0.56 μm and 1.95 ± 0.63 μm for regular and composite carrier particles, respectively were determined. The regular carrier had a higher shape value of 0.56 ± 0.17 μm which was higher than the composite carrier 0.35 ± 0.11 μm. This is understood on the basis that the composite carrier has an increased perimeter function as it is made up of many smaller sub-units rather than one crystal plane.

To determine the surface morphology of the formed carrier particles, samples of the particles were sputter coated with gold and assessed using a field emission scanning electron microscope at 10 keV (FESEM JEOL 6000, JEOL, Japan). Fig. 4 depicts the scanning electron micrographs of 63-90 micron sieve fractionated (A) raw crystalline mannitol (a control), (B) 3 micron, (C) 5 micron and (D) 10 micron composite carrier particles.

From Fig. 3, it is clear that composite carrier particles formed using different sized sub-unit particles have different morphologies and that the morphology is relatively more homogeneous than that of the raw composite material.

The surface topography of each carrier was also investigated using atomic force microscopy (AFM) (Multimode SPM with Nanoscope IIIa controller; Veeco, Cambridge, United Kingdom). Samples were mounted on carbon sticky tabs and imaged using tapping mode with a high aspect ratio silicon probe (OTESP; DI instruments, United Kingdom) over 10 μm x 10 μm areas at a scan rate of 1.0 Hz. Representative AFM topographical images of the regular and composite carrier surface are presented in Figs. 5A and 5B, respectively. In general, the regular carrier had large variations in surface topography, with linear plate-like features and irregularities consistent with various crystal growth planes. In comparison, the composite carrier had a grain-like topography with similar dome-like features on all surfaces analysed. To further quantify such observations, topographical data from 10 μm x 10 μm areas, on

multiple regular and composite particles (n = 5), were processed to obtain surface root mean square roughness (R_{RMS}) and surface areas parameters.

The surface roughness of the regular and composite particles was 0.64 ± 0.35 μm and 0.79 ± 0.09 μm, respectively. Although the composite carrier had a higher mean R_{RMS}, statistical analysis suggested no significant difference between the two carriers existed (Students t test, $p<0.05$). It is likely that this lack of significance between the surface roughnesses of the two carriers is due to the increased variability in sample morphology of the regular carrier. Such variation can be observed by comparing the relative standard deviations (RSD) of the R_{RMS} values, where the regular carrier exhibited a variance of 55%, in comparison to 11 % for the composite carrier.

To further understand the variability in carrier morphology, the projected topographical surface area of each image was divided by the sample image area (i.e. 10μm x 10μm) to obtain a projected surface area per square micron (A_{proj}). Analysis of the A_{proj} indicated values of 1.32 ± 0.19 $\mu m.\mu m^{-2}$ and 1.87 ± 0.11 $\mu m.\mu m^{-2}$ for regular and composite carrier surfaces, respectively (n=5). Statistical analysis of the A_{proj} suggested, significant differences between the two carriers (students t test, $p<0.05$). Interestingly the RSD values for the two carrier systems indicated the regular carrier to have higher variation (RSD = 15%) when compared to the composite carrier (RSD = 6%).

The force of cohesion between individual micronised salbutamol particles and carrier particles was assessed using colloid probe microscopy. Individual particles of micronised salbutamol sulphate were mounted onto the apex of nominal 0.58 N/m tipless AFM cantilevers (NP-OW, Veeco, Cambridge, United Kingdom). Particles of each carrier were mounted on carbon sticky tabs, attached to AFM sample stubs. The force of cohesion between each drug probe and both regular and composite carrier were investigated in force volume mode. 4096 individual force curves were conducted over 10 μm x 10 μm areas of each substrate using the following settings: approach-retraction cycle, 2 μm, cycle rate, 8.33 Hz, and constant compliance region of 60 nm. Each curve in the force volume matrix was analysed using custom-built software and exported as 4096 force of cohesion values for data analysis. All samples were repeated in triplicate at 45% RH and 25°C.

Since the contact area on a particular salbutamol sulphate drug probe remained constant, the variation in adhesion profiles relative to change in carrier morphology could be confidently compared.

A spatial adhesion plot of salbutamol sulphate particle adhesion with both regular and composite carriers is shown in Fig. 6. From this figure it can be seen that the adhesion of salbutamol sulphate to the regular carrier was greater than for the composite carrier, with greater variation in maximum and minimum force values. To further investigate this, the particle adhesion values were processed to produce a probability histogram. Fig. 7A shows the cumulative separation force distribution of salbutamol sulphate drug probe 1 with both regular and composite carrier particles.

Analysis of the adhesion values showed the data spread across more than one order of magnitude, in an asymmetrical positively skewed distribution. The distribution of adhesion values, in all cases, was greater for measurements on the regular carrier as observed by higher inter-quartile ranges. Analysis of the data distribution indicated that the separation forces for all samples were log-normal ($R^2 \geq 0.95$, between 5 and 95% percentiles. As a result, a median value of 50% cumulative undersize adhesion force ($f_{0.5}$) was selected as the most appropriate descriptor for particle adhesion. The $f_{0.5}$ for each salbutamol drug probe on the regular and composite carriers are shown in Fig. 7B. In general, the $f_{0.5}$ for drug interactions with the composite carrier surface was a factor of 0.48 ± 0.16 times smaller than the $f_{0.5}$ on regular carriers, suggesting reduced contact area between drug probe and surface.

To form examples of drug/carrier particle blends, the different formed carrier particles were mixed with micronised salbutamol sulphate in a ratio of 67.5:1 w/w to achieve a dose of 400µg salbutamol sulphate per every 30mg of final blend. A further blend using raw crystallised mannitol was also formed. Other drugs and ratios can be envisaged.

To determine the aerosolisation efficiency of the drug/carrier particle blends, gelatine capsules (Size three, Capsugel, Sydney, Australia) were filled with a quantity of blend (33±3 mg). Containers other than capsules can be envisaged as being suitable for the invention. A next generation impactor (NGI) (British Pharmacopoeia) was then used to characterise the aerosolisation efficiency. This determined that variation in carrier particle type had a significant effect on the aerosolisation efficiency with the

fine particle fraction (loading dose) [FPF(LD)] of the salbutamol sulphate ranging from 18.5-28.1% in the blends containing the carrier particles according to the present invention whereas the FPF(LD) of the blend containing raw mannitol carrier particles was only 5.7% (see Fig. 8). Carrier particles formed from 5 micron sub-unit particles were determined to present the best aerosolisation performance of the drug/carrier particle blends tested.

In order to evaluate the efficiency of the regular and composite carriers in aerosolising respirable drug particulates, the drug deposited on specific stages of the NGI were investigated. The drug deposition in all stages of the NGI is shown in Fig. 9. In addition, the drug deposited on stage 3 filter of the NGI is plotted along with its percentage represented as a function of the total loaded and emitted dose (referred to as the fine particle fraction of the loaded (FPF_{LD}) and emitted (FPF_{ED}) dose, respectively). These fractions (stage 3-filter) represent particles with an aerodynamic diameter of less than 4.46 μm, which would most likely penetrate the respiratory tract upon inhalation.

Analysis of the salbutamol sulphate aerosolisation efficiency from the regular carrier indicated poor drug liberation. Only 24.5 ± 12.9 μg of drug was deposited on the lower stages (3-filter), which was equivalent to an FPFLD of 5.6 ± 2.9%. Interestingly, such observations are consistent to previous studies investigating the aerosolisation of salbutamol sulphate from sieve fractioned carriers, where, salbutamol sulphate when blended with a 63-90 μm sieve fractioned mannitol produced poor FPFLD performance (9.0 ± 0.9%) when aerosolised from a Rotahaler™ (GSK). However, it is difficult to directly compare such results since the device and size distribution of materials involved differ.

In comparison to the regular carrier, the aerosolisation of salbutamol sulphate from the composite carrier was significantly higher (FPD = 78.1 ± 3.6 μg) (students t test $p<0.05$), where a FPF_{LD} of 18.5 ±_1.5% was observed. Furthermore, a reduction in aerosolisation efficiency variation was observed where an RSD for the FPF_{LD} of the composite carrier was 9% compared to 52% for the regular carrier. Such observations are in good agreement with the reduced particle adhesion observed by colloid probe microscopy, and the reduction in surface variation observed by AFM topography analysis.

In addition, high magnific ion electron micrographs of the two salbutamol sulphate-carrier formulations were taken and are shown in Fig. 10. Although, it is difficult to discriminate between drug particles and mannitol fines in the regular carrier system (Fig. 10A), the micron-sized particulates appear to have a high contact area with the planar surface of the carrier material. Furthermore, many particulates appear to be adhered in areas of potentially high adhesion (such as crevice features). In comparison, identification of salbutamol sulphate drug particles in the composite blend (Fig. 10B) is easier, since the needle-like morphology is a stark comparison to the spherical geometry of the carrier. From Fig. 9B it can be seen that the contact geometry between the drug particles is reduced due to each particle making contact with multiple mannitol sub-units. It envisaged that this formulation would result in reduced adhesion (as observed by AFM) and increased aerosolisation efficiency (as observed in the *in vitro* deposition studies).

Lactose as the Carrier Particle

Preparation of the carrier particles

Materials

Lactose monohydrate (Lactochem® crystals) was supplied by Friesland Foods Domo (Zwolle, The Netherlands). The model drug, micronised salbutamol sulphate was supplied by 3M (St. Paul, MN, USA). Water was purified by reverse osmosis (Milli-Q, Sydney, Australia) and all solvents used throughout were supplied by Biolab (Clayton, Vic, Australia) and were of analytical grade.

Preparation

A series of primary micron-sized lactose particles were prepared by spray drying an aqueous solution of lactose using a Mini Spray Dryer (Büchi, B-191, Switzerland). Spray drying conditions for each target particle diameter are shown below in table 1.

Table 1 Spray drying conditions for the preparation of primary lactose particulates

Target particle size	Inlet temperature (°C)	Measured outlet temperature (°C)	Aspiration (%)	Atomising air flow ($L.h^{-1}$)	Liquid feed rate ($ml.min^{-1}$)	Aqueous lactose solution ($g.l^{-1}$)
2 μm	150	80	100	65	5	150
6 μm	150	89	100	30	5	150
10 μm	150	97	100	20	5	200

The prepared powders were stored in a tightly sealed container with silica gel for a minimum of 24 hours prior to composite formation. After storage, the primary lactose particles were mixed with a 10% v/w saturated lactose aqueous slurry and passed through a 180 μm sieve. The resultant aggregates were dried at 150 °C for 1.5 hours in a mini fluid bed dryer (Umang Pharmatech Ltd. Easton, PA, USA). The composite powders were collected and stored for 24 hours as before, prior to sieving through a The subsequent fused aggregates were processed through a nest of sieves to produce a 63-90 μm sieve fraction. In addition, the raw starting α-lactose monohydrate was processed through the same nest of sieves to obtain a similar size fraction for comparison. Four carrier powders were produced; composites based on 2 μm, 6μm and 10 μm primary particles (referred to as 2, 6 and 10 μm carriers for ease of reference) as well as the regular carrier (sieved directly from the starting material).

Scanning electron microscopy

The morphology of the carrier particles were investigated using scanning electron microscopy (SEM). Samples were prepared by depositing on a carbon sticky tabs, mounted on a SEM stubs and sputter coated with 15-20 nm gold prior to imaging. The carrier particles were imaged at 10 keV using a field emission SEM (FESEM JEOL 6000, JEOL, Japan).

Atomic force microscopy

The topography of each carrier was studied with conventional Tapping Mode® atomic force microscopy (AFM) (Multimode AFM, nanoscope IIIa controller, Veeco Inc., California, USA). Samples were mounted on carbon sticky tabs and imaged with a high aspect ratio silicon probe (MicroMasch tips, Group Scientific Ltd, Adelaide, Australia) at a scan rate of 1.0 Hz. Three 10 μm x 10 μm areas were studied for each carrier.

Particle size analysis

The particle size distributions of the micronised salbutamol sulphate, primary lactose particles and carriers were investigated using laser diffraction. Samples were analysed using the Malvern Mastersizer 2000 with Scirocco dry powder feeder (Malvern, UK). The micron-sized powders were analysed using a 400 kPa pressure differential while the carrier systems were analysed at 100 kPa. Samples were repeated in triplicate at an obscuration between 0.3-10.0%. Refractive indices of 1.540 and 1.553 were used for lactose and salbutamol sulphate samples, respectively.

X-ray powder diffractometry

The crystalline properties of the primary lactose particles and four carriers were investigated using X-ray powder diffraction. Samples were analysed at room temperature with a XRPD D5000 (Siemens, Munich, Germany) using CuKα radiation at 30mA and 40 kV. An angular increment of $0.05°s.^{-1}$ and count time of 2 s was used.

Differential scanning calorimetry

The thermal response of the primary lactose particles and carrier systems were evaluated using differential scanning calorimetry (DSC). Approximately 10 mg of sample was accurately weighed into DSC sample pans and crimp-sealed. Samples were analysed using a DSC 823E, (Mettler Toledo, Melbourne, Australia). Samples (3-5 mg) were in DSC sample pans and thermal properties analysed at between 10 and 250°C a 10°C min-1 temperature ramp.

Colloidal probe microscopy

Colloid probe microscopy was used to measure the force of adhesion between individual salbutamol sulphate particles and each carrier. Individual particles of micronised salbutamol sulphate were mounted onto the apex of 0.58 $N.m^{-1}$ spring constant tipless AFM cantilevers (NP-OW, Veeco, Cambridge UK), using methods and validation described elsewhere. Prior to measurement, particles of each carrier were mounted on carbon sticky tabs and attached to AFM sample stubs. The force of cohesion between each drug probe and both regular and composite carrier was investigated in Force Volume mode, where 4096 individual force curves were conducted over 10 μm x 10 μm. The following settings were utilised: approach-retraction cycle, 2 μm; cycle rate, 8.33 Hz; and constant compliance region 60 nm. Each curve in the force volume matrix was analysed using custom-built software and

exported as 4096 force of cohesion values for data analysis. Three salbutamol sulphate tips were studied on each carrier at 45% RH and °C.

Preparation and characterisation of drug-carrier blends

Each 63-90μm sieve fractioned carrier was blended with salbutamol based on methods and materials described elsewhere. Briefly, salbutamol sulphate was blended geometrically with carrier at a ratio of 1:67.5, prior to a final mix in a Turbula at 46.rev^{-1} for 30 minutes. After blending samples were stored in tightly sealed containers at 45% RH and 25°C, for a minimum of 24 hours prior to analysis.

High performance liquid chromatography (HPLC) was utilised to analyse salbutamol sulphate from the in vitro aerosol performance studies and content uniformity measurements. The HPLC used was a Waters™ Millennium system (Waters Ltd., Sydney, Australia) using system components and conditions reported previously. The mobile phase used consisted of a 60:40 v/v methanol: water mixture containing 0.1% w/v sodium lauryl sulphate. Samples were dissolved in water. Linearity was obtained between 0.5 μg.ml^{-1} and 100 μg.ml^{-1} (R^2=0.9990) with a retention time of approximately 5 min. Collected samples were appropriately diluted to fit within this region.

Prior to *in vitro* aerosol evaluation of the blends, each formulation was tested for content uniformity. Approximately 33 mg of each blend was diluted with water and analysed using the HPC method described previously. Analysis of the content uniformity data suggested all formulations to have a coefficient of variance <5% (n=5).

The aerosol performance of micronised salbutamol sulphate from each drug-carrier formulation was investigated using the next generation impactor (NGI). The NGI (Apparatus E, British Pharmacopeia, Appendix XXI F) is an 8-stage inertial impactor that separates an aerosol cloud into discrete size ranges based on aerodynamic diameter. The method followed that specified for DPIs in the pharmacopoeia (Appendix XXI F). All in vitro measurements were conducted at 60 l.min^{-1}, (obtained using a Rotary vein pump and solenoid valve timer (Erweka GmbH, Germany) which was set using a calibrated flow meter (TSI 3063, TSI instruments Ltd., Buckinghamshire, UK). Prior to testing, all eight-collection stages were coated with silicon oil to eliminate particle bounce and the NGI pre-separator was accurately filled with 15 ml of purified water.

A Cyclohaler™ (Novartis, Surrey, UK) was used as a model DPI device. Approximately 33 mg of formulation was accurately weighed into a size-3 gelatine capsule (Capsugel, Sydney, Australia), which was placed into the sample compartment of a DPI. The device was activated, connected to a mouthpiece adapter, inserted into a United State pharmacopoeia (USP) throat (connected to the NGI) and tested for 4 s at 60 $l.min^{-1}$. After actuation, the device, capsule, mouthpiece adapter, throat, pre-separator and all sample stages were washed into separate volumetrics using water. Each blend was tested in triplicate.

Results from the lactose carrier particles

Particle size analysis

Size distributions of the primary particles and salbutamol sulphate are shown in fig 11 A, while the engineered carriers are shown in Fig 11 B. The salbutamol sulphate particle size distribution had a median diameter ($d_{0.5}$) of 1.39 μm ± 0.05 μm with 90% of particles ($d_{0.9}$) less than 2.71 μm ± 0.14 μm, suggesting the micronised drug to be of a suitable size for inhalation. The spray dried primary lactose particles, used to engineer the composite carriers had $d_{.05}$ diameters of 2.27 μm ± 0.12 μm, 6.15 μm ± 0.50 μm and 10.75 μm ± 0.09 μm. These particle size distributions were labelled as 2 μm, 6 μm and 10 μm, for easy reference. Analysis of the sieve fractioned carriers (Fig 11B) suggested similar $d_{0.5}$ values of 77.72 μm, 74.67 μm, 78.82 μm and 94.88 μm for the 2 μm, 6 μm, 10 μm based composite and regular carriers respectively. Such observations are expected, since the four carriers were fractioned through a 63-90 μm sieve.

Scanning electron microscopy

Representative scanning electron micrographs of the sieve fractioned composite and regular carrier particles are shown in Fig 12. All carriers appeared to have similar macroscopic morphology and size distributions. This is expected since all carriers were processed through a 63-90 μm sieve fraction. Higher resolution images showed distinct variations between the regular carrier (Fig 12 A) and the composite carriers (Fig 12 B-C). In general, the regular carrier particles were formed as discrete singular crystals of the sieve fractioned range whereas the composite carriers were macroscopically similar in dimension to the regular carrier, but were composed of multiple micron-sized particles appearing crystalline in nature. In addition, qualitative analysis of the composite carriers suggested an increase in micro-particle morphology between the 2

μm and 10 μm based composite carriers, respectively. However, it is interesting to note, that the individual particles making up the composite (particularly, for example, in the larger 10 μm-based carriers) did not have a similar diameter to the median $d_{0.5}$ of the primary particles, measured by laser diffraction. Such observations can be explained by the re-crystallisation of the primary particles during the drying process. To further quantify the variations in surface morphology, atomic force microscopy was utilised to study the surface topography of each carrier.

Atomic force microscopy

Representative topographical images of the composite and regular carriers are shown in Fig 13 A-D. Clear variations in the topography could be observed across the carrier types. Specifically, the regular carrier (Fig 13 A) had a smooth planar morphology while the composite materials were granular in nature; most likely due to the individual microparticles which make up their construction. To further evaluate these variations the root mean square roughness (R_{RMS}) for each image (n=3) was calculated using Equation 1.

Equation 1 $$R_{rms} = \sqrt{\frac{1}{n}\sum_{i=1}^{n} y_i^{\,2}}$$

Analysis of the R_{RMS} suggested the carriers followed the rank order 2 μm > 6 μm > 10 μm composite carriers > regular carrier. Specifically, analysis of the R_{RMS} indicated significantly different values of 0.50 nm ± 0.01 nm, 0.36 nm ± 0.01 nm, 0.32 nm ± 0.01 nm and 0.09 nm ± 0.05 nm for 2 μm, 6 μm, 10 μm composite carriers and regular carrier, respectively. Such observations suggest that variation in primary particle size has a significant effect on the composite particle roughness.

X-ray powder diffractometry

X-ray powder diffractograms of the primary lactose particles and carriers are shown in Fig 14 A and B, respectively. The diffuse diffraction patterns for the primary lactose particles (Fig 14 A) are indicative of an amorphous material. In comparison, the diffraction patterns for the carrier materials had intensity patterns characteristic of crystalline material. In general, the diffraction patterns for the carrier materials (Fig 14 B) were similar and had peaks characteristic of α-lactose monohydrate at 12.4° 2θ. The composite carrier diffraction patterns had intensities less than that of the regular carrier,

most likely due to the significant difference in the primary crystal size (2-10 μm in comparison to 63-90 μm). Interestingly, the composite carriers had an additional peak at 10.6° 2θ, suggesting the presence of β-lactose which is produced due to the mutarotation of the α-form during the drying process.

Differential scanning calorimetry

Differential scanning thermograms for the four primary lactose particles and four carriers are shown in Fig 15 A and B, respectively. As expected, the thermal response for the primary particles was indicative of an amorphous material. Specifically, an exothermic peak for each powder was observed with an onset between 130-140°C. This is similar to previous reports for re-crystallisation of amorphous lactose. Interestingly, the onset increased with increasing median particle temperature. It is suggested that this increase is due to an increase in heat capacity and reduction in surface area to mass ratio. In comparison, the thermal response of the carrier materials (Fig 15 B) were characteristic of crystalline material. For all samples, an endothermic peak was observed between 140-150°C which could be attributed to the heat of dehydration from α-lactose monohydrate. In addition, comparison of the regular and composite carrier suggested different endothermic peaks at 216°C for the regular and peaks at 216°C and 235°C for the composite carriers. These peaks at 216°C and 235°C correspond to the α-lactose monohydrate and β-lactose, respectively. Such observations suggest that the composite carriers were a mixture of both α-lactose monohydrate and β-lactose, most likely due to the mutorotation of the α-form during the drying stage.

Colloidal probe microscopy

Adhesion data collected between each salbutamol sulphate drug probe (n=3 probes x 4096 force measurements over 10 x 10 μm areas) were processed to produce median force values ($f_{0.5}$) and percentile under-force values. The processing methodology followed that for log-normal force distributions as described previously. In addition the spread of force values was calculated from the geometric standard deviation:

Equation 2 $$GSD = \left[\frac{f_{0.84}}{f_{0.16}}\right]^{0.5}$$

Where f_x are the respective percentile force values for the lognormal distribution. Essentially a GSD of 1 would be a monomodal, monodispersed force distribution.

Analysis of the adhesion data suggested significant differences in adhesion force between the salbutamol sulphate drug probes (n=3) and the different carriers. In general, the median adhesion force followed the rank order: 2 μm composite carrier < 6 μm composite carrier < 10 μm composite carrier < regular carrier. Specifically, median adhesion forces (± standard deviations) of 30.15 nN ± 0.75 nN, 33.31 nN ± 6.32 nN, 46.43 nN ± 3.83 nN and 113.11 nN ± 15.10 nN were observed for the 2 μm, 6 μm, 10 μm composite carriers and regular carrier, respectively. Post-hoc analysis suggested the variation in adhesion to be significant between all paired and unpaired samples except for the 2 μm and 6 μm paired analysis. Such observations are most likely due to the large standard deviation in adhesion forces on the 6 μm based carrier. Since variation in adhesion across the surface may be directly related to the propensity for drug liberation during aerosolisation, the GSD for each data set was calculated and processed to represent mean GSD values (± standard deviations) and are shown along representative adhesion maps in Fig 16. The degree of colour variation in Fig 16 indicates the distribution in force values. Analysis of the mean GSD, suggested a rank order of 2 μm < 10 μm < 6 μm < regular based carrier systems Furthermore, analysis of the GSD between samples (n=3 carrier measurements) resulted in a greater variation in the 6 μm and regular carriers, where a coefficient of variation (CV) of 15.1% and 10.5% was observed, respectively. In comparison, the 2 μm and 10 μm carriers exhibited reduced adhesion value distributions

in vitro aerosol characterisation

The drug recovered from all components of the NGI and device was measured by HPLC as previously described and the data was processed to produce various descriptors of aerosolisation efficiency. These were the total recovered dose from the device and all NGI components (TD); the emitted dose (ED), representing TD excluding capsule and device components; the fine particle dose (FPD) representing drug recovered from stage 3 to 8 of the NGI (equivalent to the mass of particles with an aerodynamic diameter < 4.46 μm). In addition, the percentage drug deposited on each stage was calculated for each formulation and is plotted in Fig 17. Analysis of the total TD and ED suggested no significant differences with recoveries of 514.9 μm ± 44.8 μm and 431.7 μm ± 32.5 μm being observed across all formulations. Subsequently, no

variations in drug removal efficiency were observed (ED/TD x 100). An efficiency of 84% ± 6% across all formulations was in good agreement with previous findings. Since the efficiency remained constant it may be assumed that the any variation in FPD may be due to drug carrier detachment during aerosolisation and not due to formulation segregation prior to analysis. This is further substantiated by the content uniformity results, which showed all formulations to have a CV less than 5%.

Analysis of the percentage stage deposition (Fig 17) showed the regular carrier had less drug deposited on the lower stages with the majority being captured on the pre-separator. High depositions on the pre-separator stage may be associated with drug still adhered to carrier after the aerosolisation process. In comparison, the deposition profiles of drug from the composite carrier systems indicated higher depositions in the lower stages of the NGI suggesting improved aerosol performance. To further analyse the relationship between carrier type and aerosolisation efficiency, the fine particle fraction was calculated based on the ED (where FPF = FPD/ED x 100). Analysis of the FPF data suggested the carrier type to have a significant affect on the aerosolisation performance where the FPF varied between 21.3% ± 5.4% to 31.3% ± 1.3% between regular lactose and the 2 μm composite lactose, respectively. In addition, analysis of the standard deviations of the FPFs from each formulation suggested variability (CV) to be dependent upon formulation type where FPF CV's of 4%, 13%, 5% and 25% were observed for the 2 μm, 6 μm, 10 μm and regular carrier, respectively.

Relationship between drug aerosol performance and the physico-chemical parameters of the carrier systems

To further understand the relationship between the different carrier systems and drug aerosol performance, the FPF was investigated in terms of each of the physico-chemical parameters studied. One of the primary differences between the regular and composite carriers was the presence of β-lactose in the composite samples. Interestingly, there was still variation in the FPF in the composite samples although the heat of dehydration remained constant. Such observations indicate that particle morphology plays an important role in the aerosolisation phenomena. Furthermore, previous studies have suggested that β-lactose results in significantly poorer aerosolisation performance than α-lactose monohydrate. In this previous study, formulations containing micronised salbutamol sulphate were used with identical formulation and testing protocols. Subsequently, it may be concluded that in this study,

while there was variation in carrier chemistry, the variation between the regular and composite carriers is more dependent on morphology.

Evaluation of the topographic roughness suggested significant differences between the carrier particles. To investigate the relationship between roughness and aerosolisation performance, the FPF was plotted as a function of R_{RMS} and is shown in Fig 18. Regression analysis of the FPF vs. R_{RMS} indicated a positive linear relationship with an R^2 value of 0.9672. Such an increase in FPF with respect to roughness may be related to the reduced contact area between drug particles and carrier surface.

As previously discussed, a reduction in drug-carrier contact area would result in reduced inter-particle adhesion. To investigate the relationship between aerosolisation efficiency and drug-carrier adhesion, the FPF was plotted vs. the median adhesion force values and are shown in Fig 19. An inverse relationship between FPF and the median adhesion force was observed, with a regression coefficient of $R^2 = 0.9658$ (similar to that for the FPF-roughness analysis). It may be concluded that a clear relationship exists between contact area (in this case measured by a R_{RMS} roughness parameter), drug-carrier adhesion and aerosol performance. In addition, it is interesting to note, the relationship between the standard deviation of the FPF measurements and the geometric standard deviation of the adhesion measurements. For example, a large standard deviation is associated with the FPF of drug from the 6 μm composite carrier even though content uniformity was <5% and the aerosolisation efficiency was not significantly different than the other carrier systems. Subsequently, it may be concluded that the variation in FPF is due to a wider distribution in the adhesion force between drug and carrier on the surface. Indeed, analysis of the median adhesion forces for drug on the 6 μm composite carriers had a greater standard deviation than for the other composite systems (Fig 19). Such observations are further substantiated when studying the GSD values for the adhesion measurement (indicative of data spread) and the CV associated with multiple area analysis (Fig 16). As expected, larger variations in adhesion and FPF were found in the regular carrier, which could be associated to the poorer FPF and standard deviation.

The above experiments with lactose show how a series of crystalline composite carriers can be prepared from smaller sub-units of lactose. The surface morphology and physico-chemical properties of the composite carriers were significantly different than regular α-lactose monohydrate. Depending on the initial primary lactose size, the

composite particles could be prepared with different surface roughness. Variation in composite roughness could be related to the potential change in drug adhesion (via modification in contact geometry) and thus drug aerosol performance from drug-lactose blends. Although, in all cases the composite carriers resulted in improved drug aerosol performance, it should be noted that the distribution of adhesion potential across each carrier was specific to the primary size. Thus it may be concluded that, careful selection of surface roughness is required to optimise aerosol performance and reduce the variability in respiratory delivery.

A schematic of the likely influence of morphology on the relative contact area between drug and carrier is shown in Fig. 20.

The production of a carrier containing a surface constructed of smaller units (composite) allows control of the surface morphology. Specific inter-particular 'gaps' between the individual components of the composite may result in variations in geometry and surface roughness. This can subsequently influence the contact geometry between drug and carrier; thus influencing adhesion and aerosol performance. By choosing different sized sub-units the degree of adhesion may be tailored to the specific drug particles used. Furthermore, the use of smaller sub-units to make up the carrier results in a morphology which is more consistent on the micro and nanoscopic levels

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

CLAIMS:

1. An inhalable drug carrier particle for carrying at least one drug particle, formed from a plurality of adhered or otherwise co-joined sub-unit particles, wherein the sub-unit particles have an average size of between about 20nm and about 20 microns.

2. The drug carrier particle of claim 1 wherein the carrier particle is formed from sub-unit particles being each of substantially the same size.

3. The drug carrier particle of claim 1 or claim 2 wherein the sub-unit particles have an average size of less than about 12 microns.

4. The drug carrier particle of any one of the preceding claims wherein the formed drug carrier particle has an average size of between about 50 to about 250 microns.

5. The drug carrier particle of any one of the preceding claims wherein the drug carrier particle has a substantially homogeneous surface.

6. The drug carrier particle of any one of the preceding claims wherein the average size of the sub-unit particles is less than about 300% of the average size of the drug particle.

7. The drug carrier particle of any one of the preceding claims wherein the average size of the sub-unit particles is about the same size or smaller than the average size of the drug particle.

8. The drug carrier particle of any one of the preceding claims wherein at least about 50% of the sub-unit particles have an average size of between about 20nm and about 20 microns.

9. The drug carrier particle of any one of the preceding claims wherein the carrier particle is formed of sub-unit particles of any suitable material, including one or more sugars including monosaccharides, disaccharides, polysaccharides such as arabinose, glucose, fructose, ribose, mannose, sucrose, trehalose, lactose, maltose, dextran, starches or sugar alcohols such as mannitol or sorbitol and mixtures of two or more thereof.

10. A method of forming an inhalable drug carrier particle comprising:

a) particle engineering a substance to form sub-unit particles;

b) adhering or otherwise co-joining the sub-unit particles to form the drug carrier particle.

11. A method of forming an inhalable drug carrier particle for carrying at least one drug particle, said method comprising:

a) using sub-unit particles with an average size of less than about 300% of the average size of the drug particle;

b) adhering or otherwise co-joining the sub-unit particles to form the drug carrier particle.

12. The method of any one of claims 8 to 11 wherein the carrier particle has the features of any one of claims 1 to 9.

13. An inhalable drug carrier particle formed from a plurality of adhered or otherwise co-joined sub-unit particles, wherein the drug carrier particle has an average size of about 50 - 250 microns.

14. An inhalable drug carrier particle formed from a plurality of adhered or otherwise co-joined particle engineered sub-unit particles.

15. An inhalable drug carrier particle for carrying at least one drug particle, said drug carrier particle formed from a plurality of adhered or otherwise co-joined sub-unit particles, wherein the average size of the sub-unit particles is less than about 300% of the average size of the drug particle.

16. An inhalable drug carrier particle for carrying at least one drug particle, said drug carrier particle formed from a plurality of adhered or otherwise co-joined sub-unit particles, wherein the average size of gaps between the co-joined sub-unit particles on the surface of the drug carrier particle is less than the average size of the drug particle.

17. The drug carrier particle of any one of the preceding claims wherein the average size is the median diameter.

18. A drug/carrier particle blend formed from drug carrier particles according to any one of the preceding claims.

19. A method of delivering a drug to a patient requiring the drug, the method comprising forming a drug/carrier particle blend according to claim 18 and aerosolising the blend such that it is suitable for inhalation by the patient.

20. A method of treating a patient having a respiratory or non-respiratory condition, said method comprising administering the drug/carrier particle blend according to claim 18.

21. Use of the drug/carrier particle blend according to claim 18 for the manufacture of a medicament for the treatment of a respiratory or non-respiratory condition of a patient.

22. Use of the drug/carrier particle blend of claim 21 wherein the respiratory condition is selected from the group comprising COPD, bronchitis, allergy, rhinitis, cystic fibrosis, pulmonary infection and asthma.

23. A drug carrier particle, method or use substantially as hereinbefore described with reference to the accompanying figures.

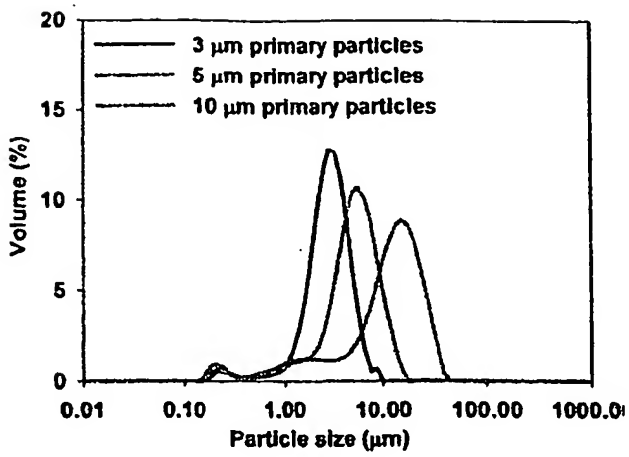

3 µm primary particles
5 µm primary particles
10 µm primary particles
Volume (%)
20
15
10
5
0
0.01
0.10
1.00
10.00
100.00
1000.0
Particle size (µm)

Fig. 1

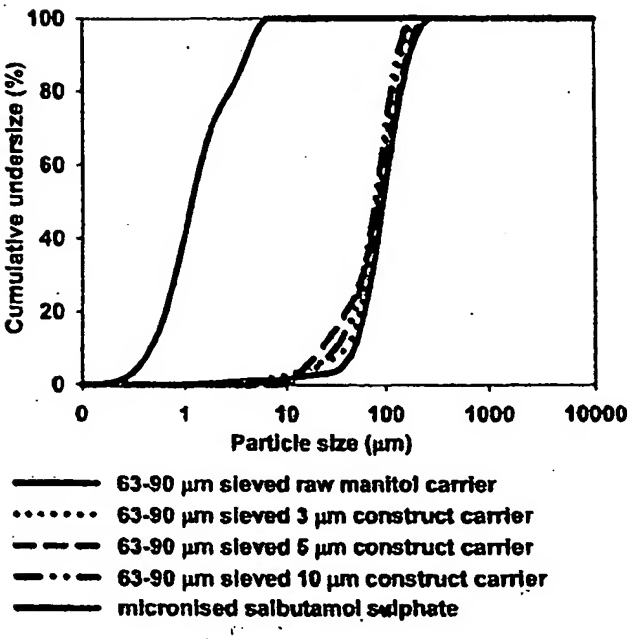
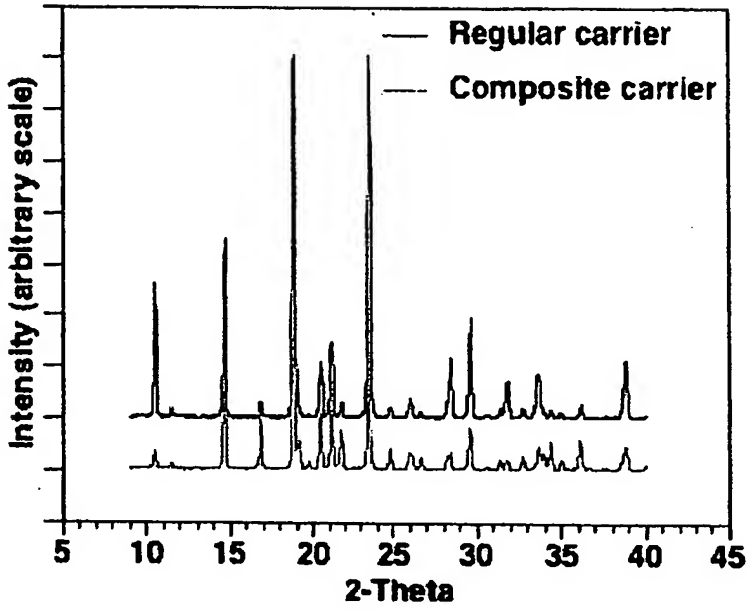

Cumulative undersize (%)
100
80
60
40
20
0
0
1
10
100
1000
10000
Particle size (µm)
63-90 µm sieved raw manitol carrier
63-90 µm sieved 3 µm construct carrier
63-90 µm sieved 5 µm construct carrier
63-90 µm sieved 10 µm construct carrier
micronised salbutamol sulphate

Fig. 2

Figure 3 X-ray powder diffraction patterns of the regular and composite carrier particles.



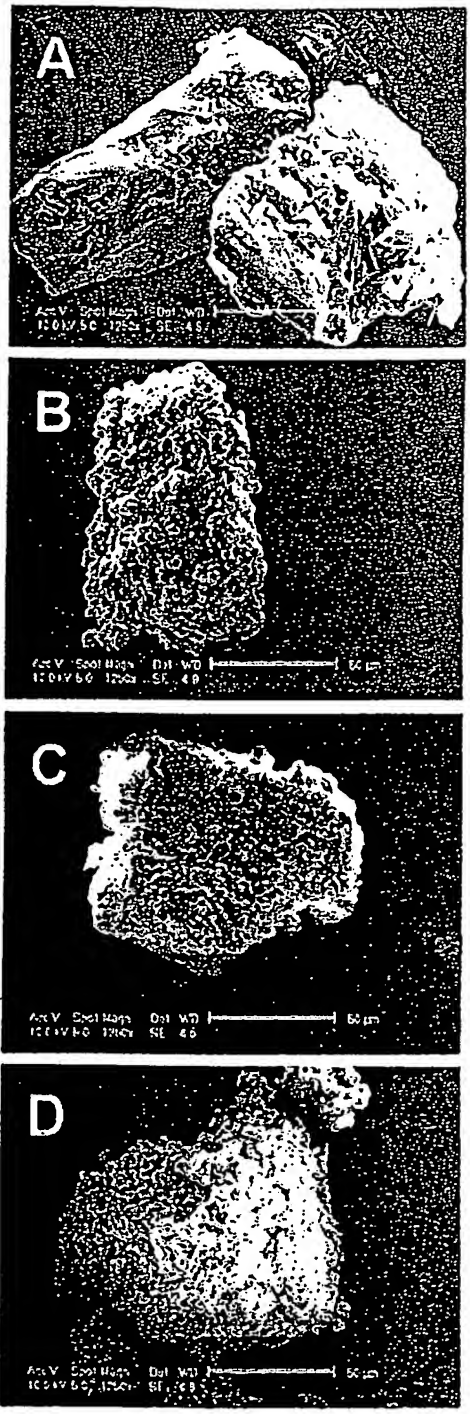


FIG. 4

Figure 5 Representative atomic force microscope topography image of (A) regular carrier and (B) composite carrier

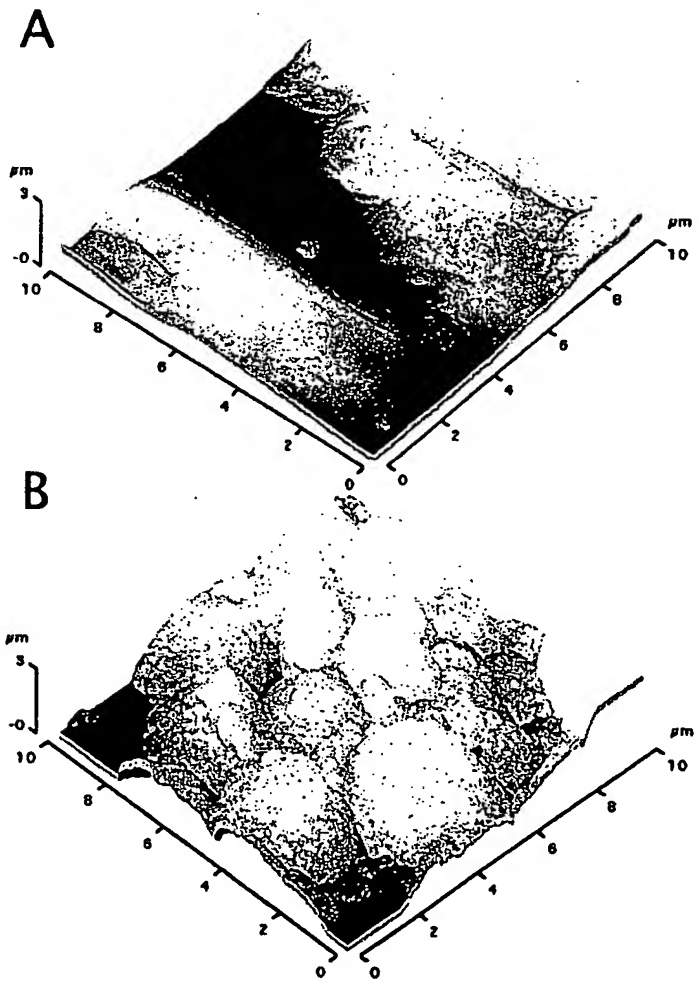


Figure 6 Spatial adhesion distribution of salbutamol sulphate drug probe 1 over 10 x 10 μm areas of a regular and composite carrier.

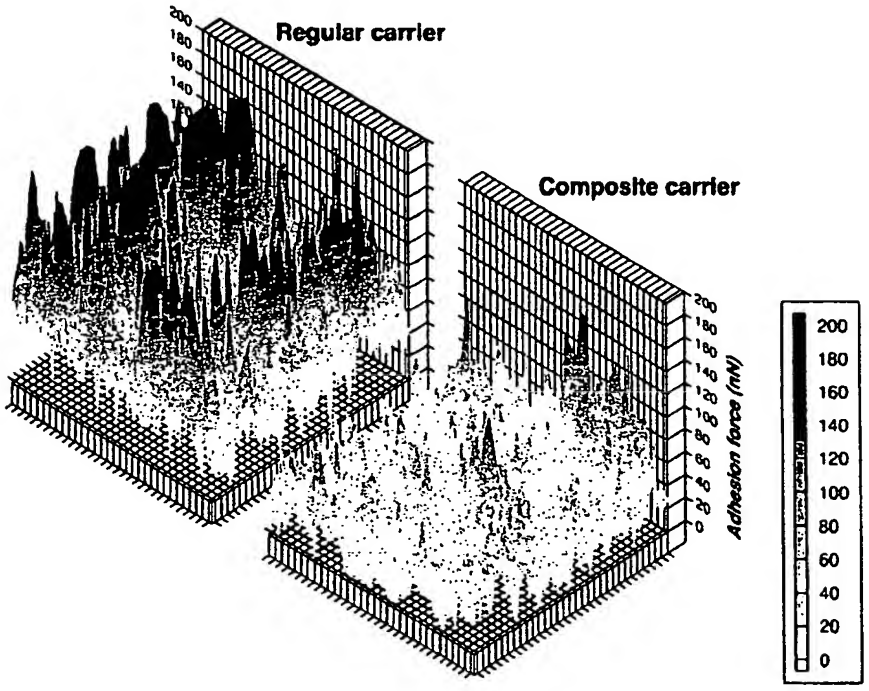
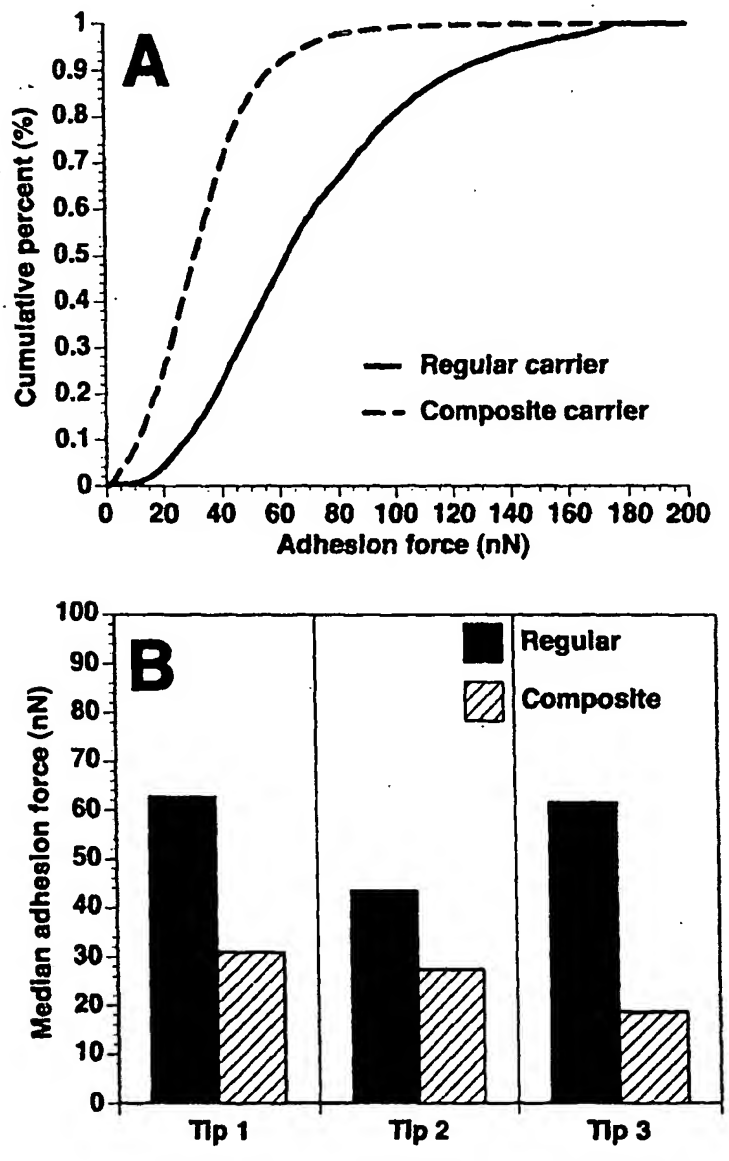


Figure 7 (A) Cumulative percentage adhesion plot for salbutamol AFM probe 1 measured over a 10 μm x 10 μm area on a regular and composite carrier (as in Figure 5); (B) median separation force of three probes on both carrier substrates.



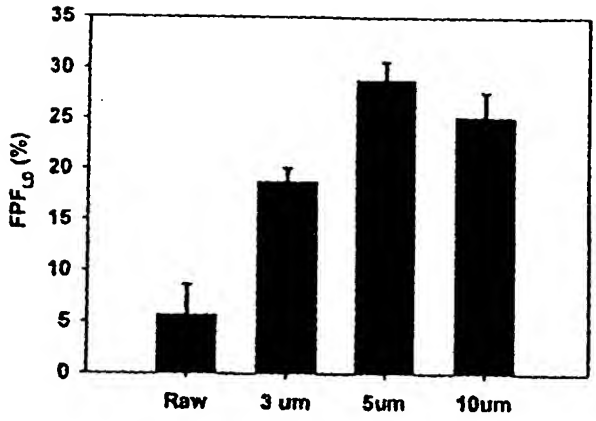


Fig. 8

Figure 9 Next generation impactor stage deposition of salbutamol sulphate aerosolised from blends containing each of the carriers.

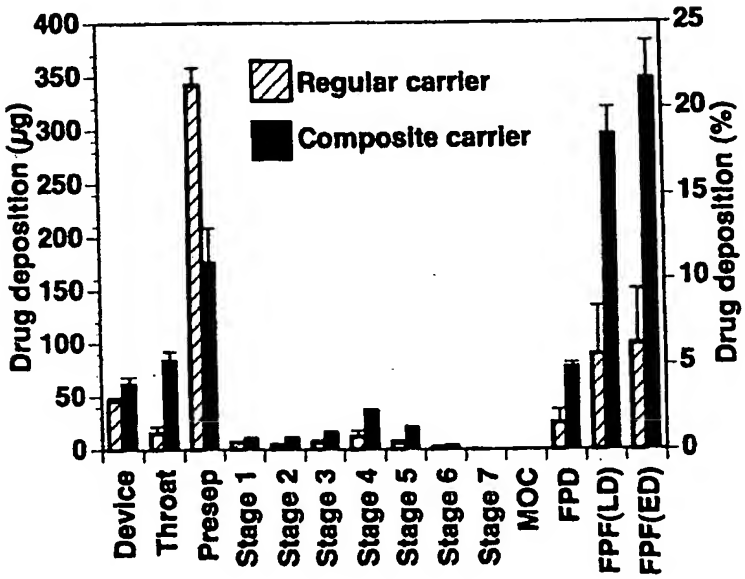


Figure 10 High magnification SEM images of (A) regular carrier blend and (B) composite carrier blend. Arrows point to likely salbutamol sulphate particulates.

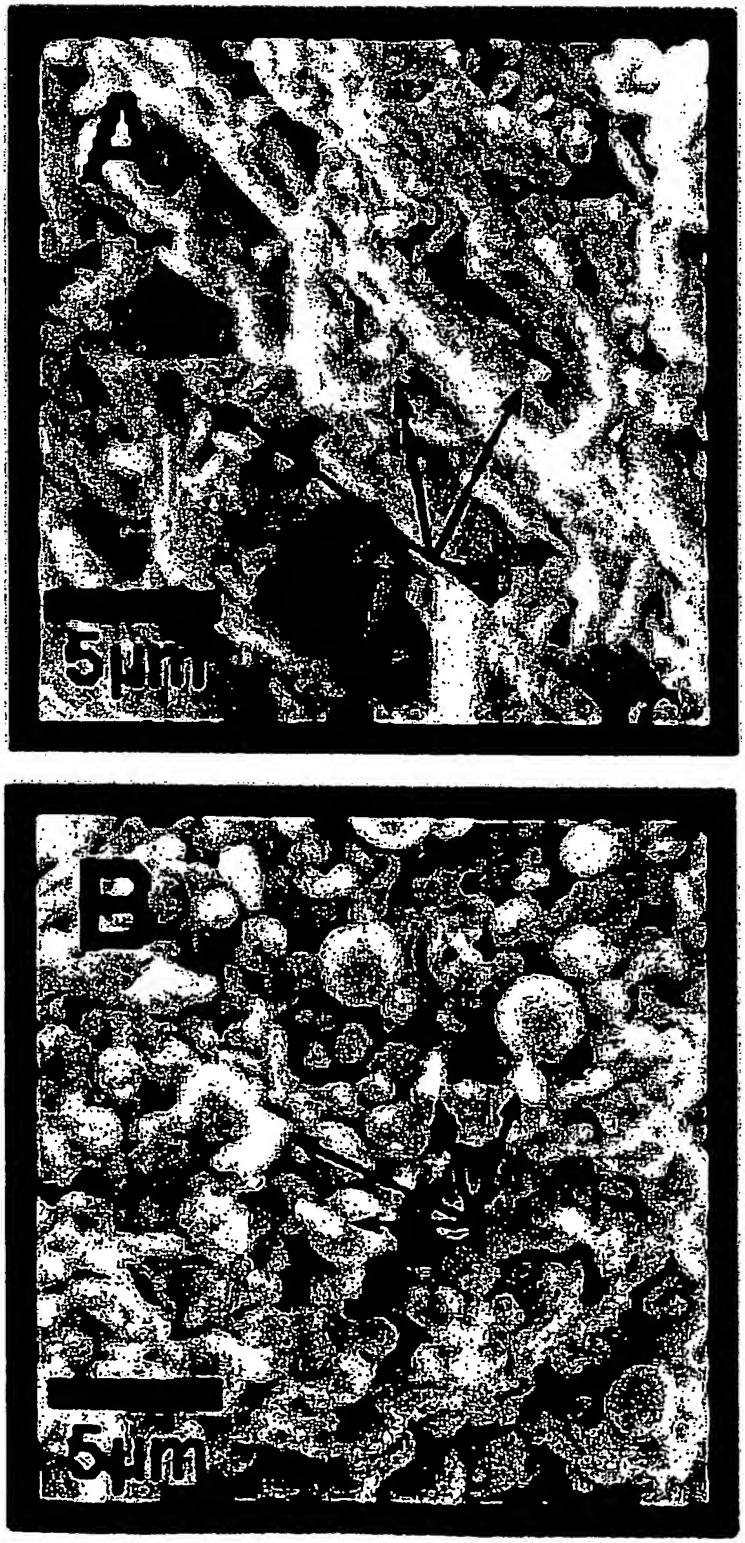


Figure 11 **Particle size distributions of the (A) micronised drug samples and primary lactose particles, (B) carrier particles**

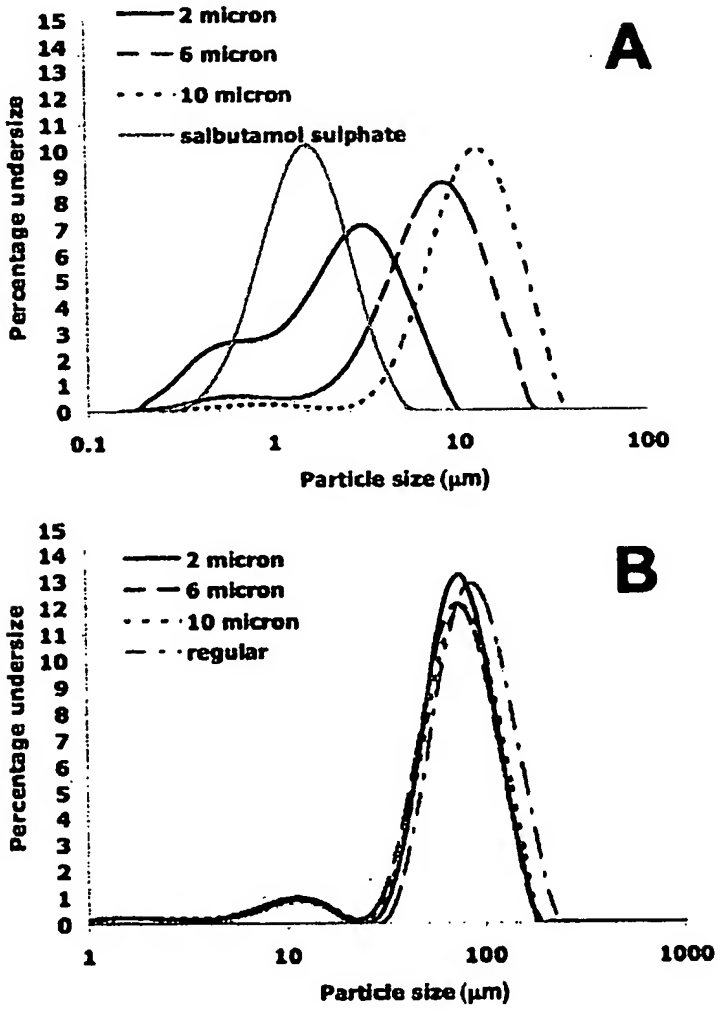


Figure 12 **Scanning electron microscopy images of fractioned (A) regular carrier, (B) 2 μm based carrier, (C) 6 μm based carrier and (D) 10 μm based carrier**

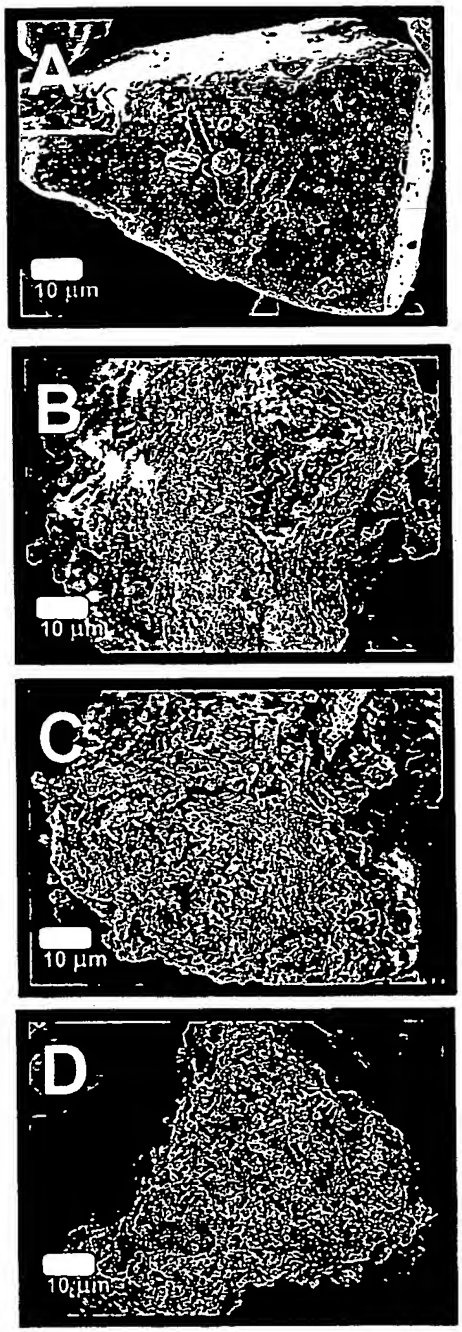


Figure 13 Representative topographical images of the 63-90 μm sieve fractioned (A) regular carrier (B) 2 μm based carrier (C) 6 μm based carrier and (D) 10 μm based carrier

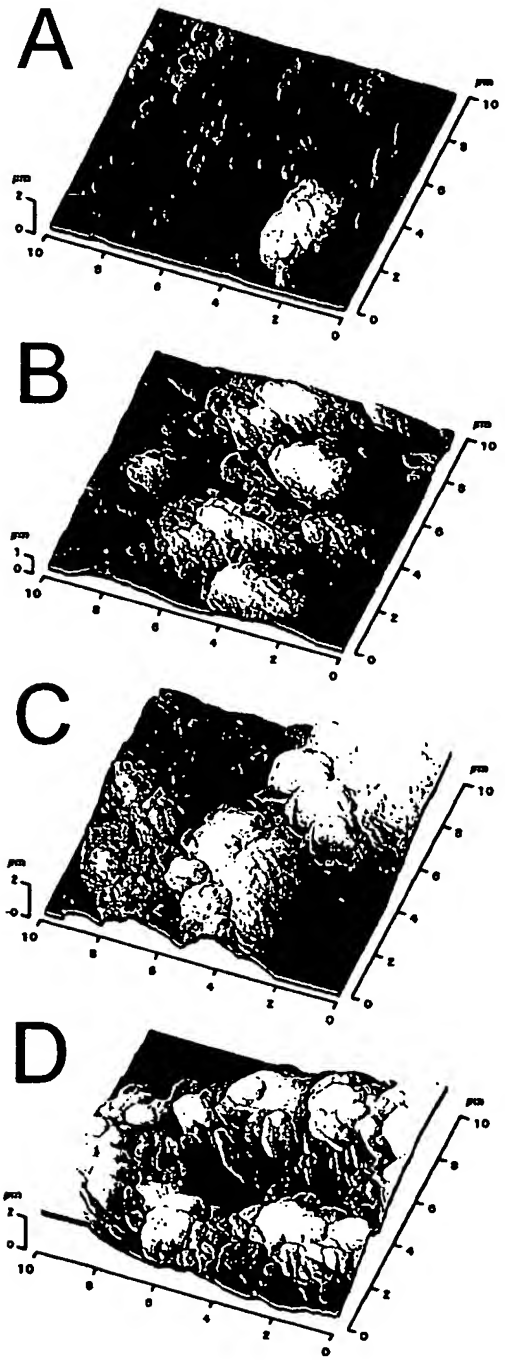


Figure 14 X-ray powder difractographs for the (A) primary lactose particles and (B) carriers.

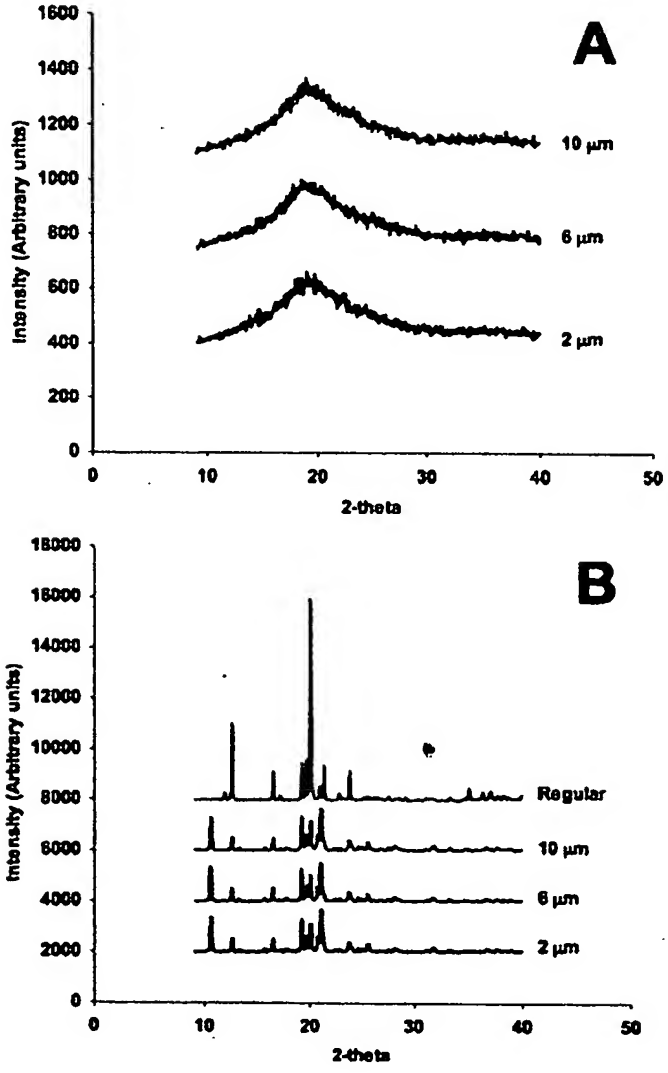


Figure 15 **Differential scanning calorimetry thermograms of (A) primary lactose particles and (B) carriers**

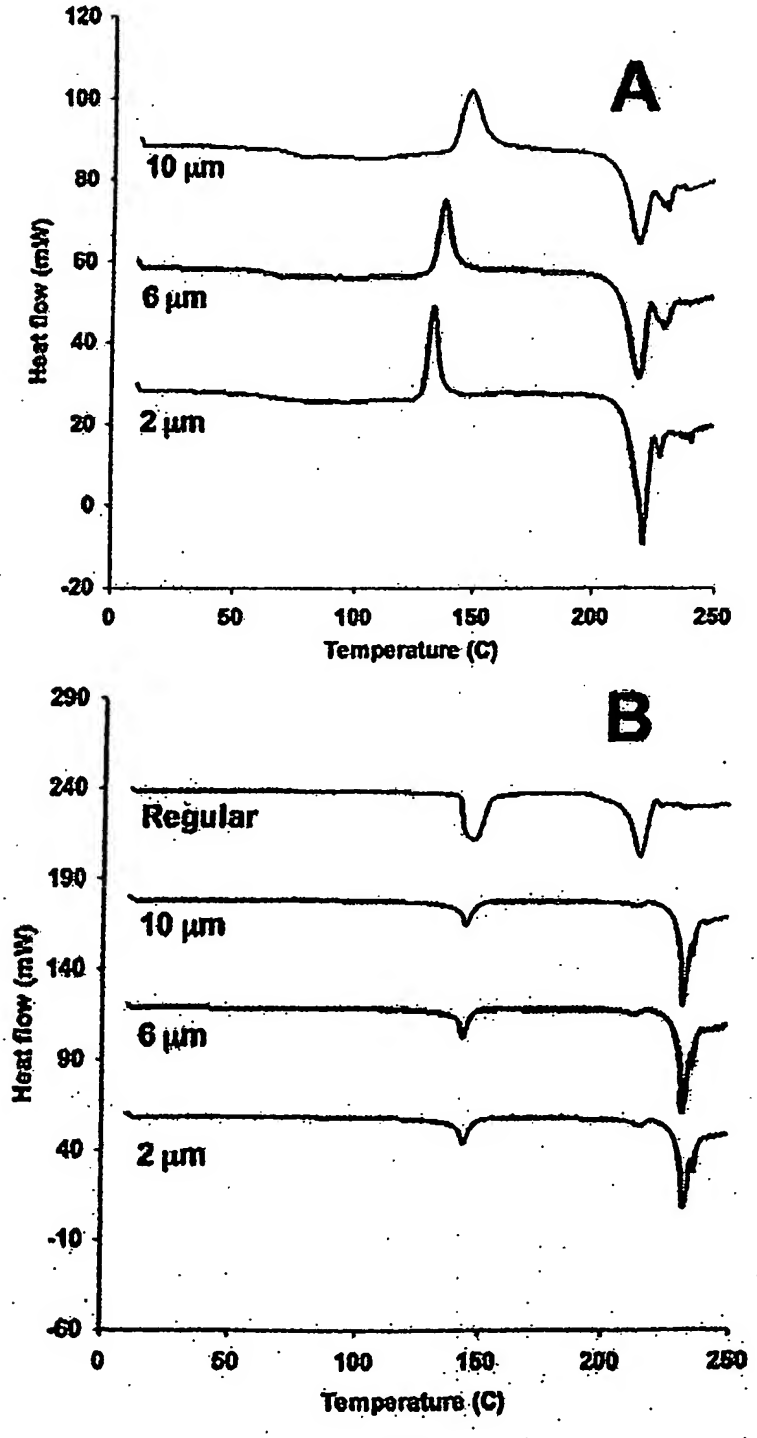


Figure 16 **Adhesion distribution matrix (10 μm x 10 μm areas) for a single salbutamol probe on each carrier lactose. Mean GSD values are given for n=3 probes with standard deviations and % CV**

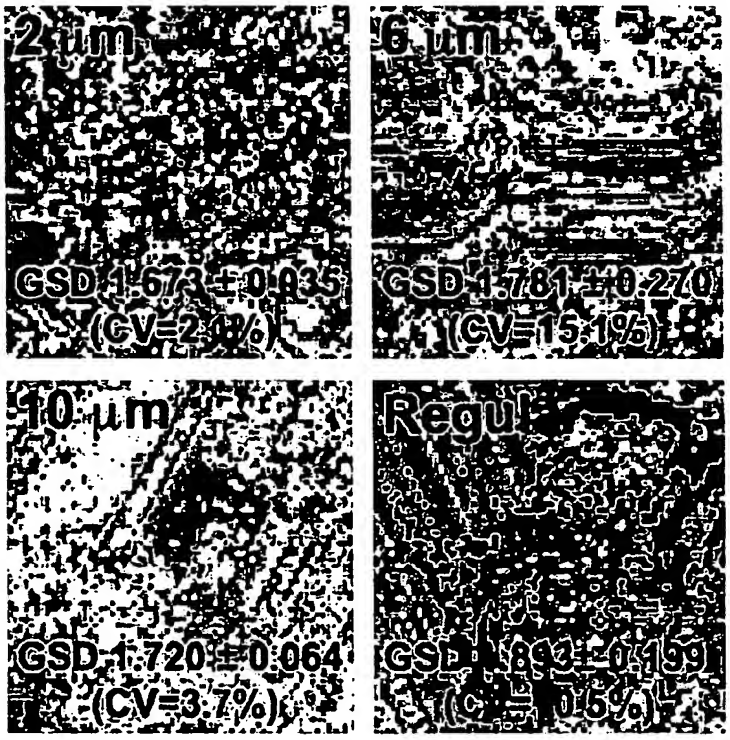


Figure 17 ***in vitro*** **NGI stage deposition of salbutamol sulphate aerosolised from each of the carriers**

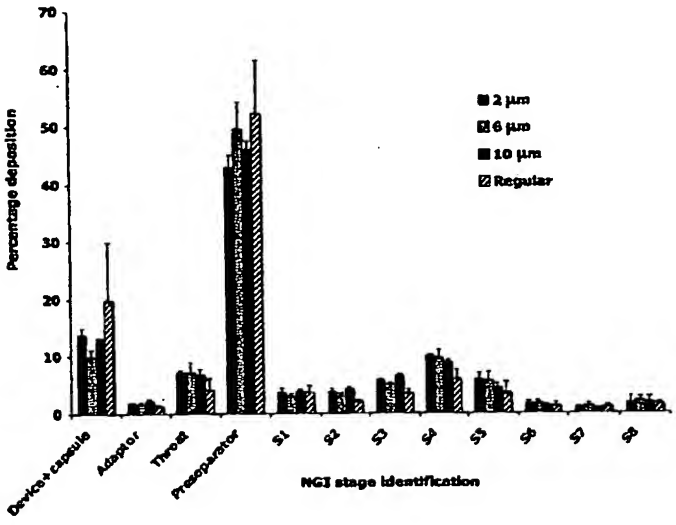


Figure 18 ***in vitro*** **aerosol performance (FPF) as a function of roughness (R_{RMS}). Error bars indicate standard deviations (n=3)**

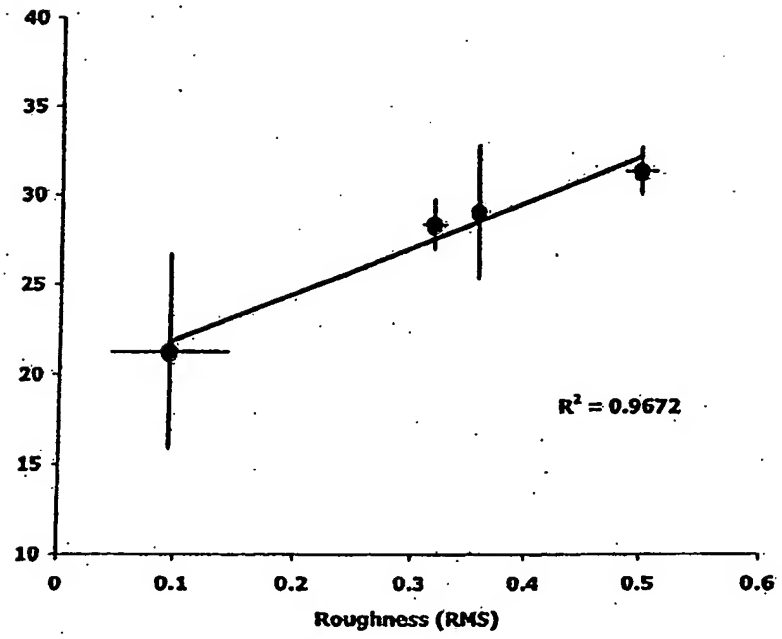
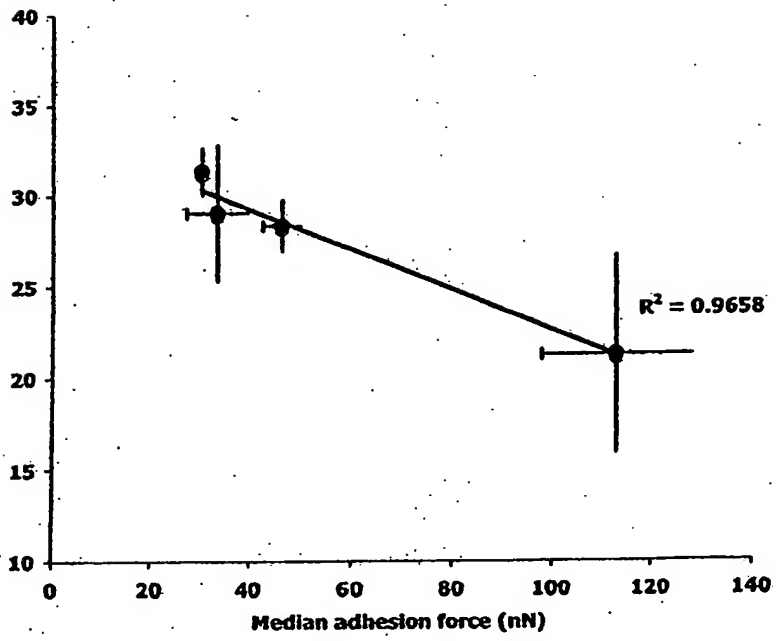


Figure 19 **Relationship between median adhesion force (n=3 tips ± StDev) and the aerosol efficiency (FPF%, n=3).**



Smooth carrier: high contact area:
Pros: good blend content uniformity
Cons: increased adhesion - decreased drug liberation

Commercial grade carrier: variation in contact area:
Pros: commercially produced - low cost
Cons: contact area variation - drug liberation variation

Microscopic roughness: high contact area:
Pros: consistent adhesion profile - good content uniformity
Cons: increased adhesion & decreased drug liberation

Ideal morphology: reduced contact area:
Pros: consistent adhesion profile - controllable adhesion (through void space) - good content uniformity - good drug liberation

Nanoscopic roughness: low contact area:
Pros: increased liberation - decreased adhesion
Cons: poor content uniformity - blend segregation

Fig. 20.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2008/000630

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

A61K 47/26 (2006.01) *A61K 9/14* (2006.01) *A61P 11/00* (2006.01)
A61K 9/12 (2006.01) *A61K 9/72* (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 47/26

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPIDS, Medline, CA, EPODOC, WPI, Google Patents, Scirus: inhalation, respiratory, aerosol, pulmonary, lung, breath, carrier, monosaccharide, disaccharide, polysaccharide, arabinose, glucose, fructose, ribose, mannose, sucrose, trehalose, lactose, maltose, dextran, starch, sugar alcohol, mannitol, sorbitol, particle, aggregate, drug, pharmaceutical, medicament, salmeterol, salbutamol, luticasone propionate, formoterol, budesonide, beclomethasone dipropionate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6103270 (JOHNSON, K.A. ET AL)15 August 2000 Whole Document	
A	WO 2002045682 A1 (SCHOOL OF PHARMACY, UNIVERSITY OF LONDON) 13 June 2002 Whole Document	
A	US 6309623 B1 (WEERS, J.G. ET AL) 30 October 2001 Whole Document	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
17 June 2008

Date of mailing of the international search report
01 JUL 2008

Name and mailing address of the ISA/AU

AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606, AUSTRALIA
E-mail address: pct@ipaustralia.gov.au
Facsimile No. +61 2 6283 7999

Authorized officer
MS CORRINA PARKER
AUSTRALIAN PATENT OFFICE
(ISO 9001 Quality Certified Service)
Telephone No : (02) 6222 3661

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2008/000630

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6153224 (STANIFORTH, J.N.) 28 November 2000 Whole Document	
A	WO 2004017914 A2 (IVAX CORPORATION ET AL) 4 March 2004 Whole Document	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2008/000630

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	6103270	AU	59643/96	CA	2224064	EP	0831782
		MX	9709448	US	5654007	US	5922354
WO	2002045682	AU	22145/02	EP	1339388	US	2004062719
US	6309623	AU	10644/99	AU	11857/99	AU	35469/99
		AU	59637/01	AU	61246/01	AU	61669/01
		AU	96770/98	AU	96772/98	AU	2003300137
		AU	2003302274	AU	2005258040	AU	2006222737
		BG	104253	BR	0317810	BR	9812693
		BR	PI0512326	CA	2304819	CA	2304820
		CA	2304973	CA	2304975	CA	2335940
		CA	2382133	CA	2408464	CA	2432319
		CA	2511523	CA	2511555	CA	2567785
		CN	1272058	CN	1741789	EE	200000194
		EP	1019020	EP	1019021	EP	1019022
		EP	1019023	EP	1091755	EP	1280520
		EP	1282405	EP	1286715	EP	1343372
		EP	1581182	EP	1589947	EP	1773301
		HK	1031680	HR	20000175	HU	0002478
		HU	0500846	IS	5415	KR	20050088242
		KR	20050095838	MX	PA02001323	MX	PA02011003
		MX	PA03005655	MX	PA05007156	MX	PA05007158
		NO	20001618	NO	20053076	NZ	503464
		PL	339732	PL	378270	SK	4492000
		US	2001046474	US	2002000225	US	2002017295
		US	2002037316	US	2002177562	US	2002187106
		US	2002188281	US	2003003057	US	2003064029
		US	2004105820	US	2004156792	US	2004170568
		US	2004176391	US	2005056276	US	2005074498
		US	2005207986	US	2006025355	US	2006159625
		US	2006159629	US	2006165606	US	2007123477
		US	2007212405	WO	0000215	WO	0185136
		WO	0185137	WO	0193932	WO	9916419
		WO	9916420	WO	9916421	WO	9916422
		WO	02054868	WO	2004060351	WO	2004060903

		WO	2006002140	ZA	200505155		
US	6153224	AU	45456/96	BG	101858	BR	9607490
		CA	2211874	CN	1179097	CZ	9702443
		EE	9700176	EP	0806938	EP	1159955
		EP	1232745	EP	1666023	FI	973151
		HU	9802209	IS	4531	MX	9705847
		NO	973502	NZ	300654	PL	321572
		SK	103697	US	6153224	US	2003170183
		US	2006029552	WO	9623485	ZA	9600721
WO	2004017914	AU	2003260049	AU	2003269989	CA	2499273
		CA	2499280	EP	1560567	EP	1599209
		KR	20050083648	KR	20050088276	MX	PA05001901
		MX	PA05001903	NO	20051461	NO	20051463
		NZ	538963	NZ	538965	US	2004258626
		US	2005158248	WO	2004017942	ZA	200502172
		ZA	200502177				

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX